Neurocognitive impairments and prefrontal brain functioning in individuals at risk for schizophrenia and bipolar disorder: A first step in search for potential biomarkers

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Summary

Early recognition of schizophrenia and bipolar disorder has been a popular and important research topic in the last years. Even though the early symptoms of these disorders may emerge in adolescence, the disorders themselves usually remain un- or misdiagnosed for up to several years. Research has shown that this delay in treatment or a wrong treatment all together may have a negative impact on the course of a disorder. Therefore, several early recognition programs aim at identifying individuals at risk for schizophrenia and bipolar disorder before the disorders beome fully manifest.

The early recognition programs are mostly based on assessment of various constellations of psychopathological symptoms. However, many of these symptoms, as well as other risk factors, are simultaneously predictive for many psychiatric disorders, making the early recognition processes difficult. Therefore, objectively measureable biological markers indicating the presence, absence or stage of a disorder are being searched for. Despite the intense research, no biomarker with sufficient sensitivity and specificity has been found until now. The aim of this dissertation was to investigate the frontal brain functioning in the individuals at risk for schizophrenia and bipolar disorder and through that contribute to the early recognition research.

The data used in this dissertation were gathered within the framework of the Zurich Program for Sustainable Development of Mental Health Services (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie, ZInEP), subprojects 2 and 6. Subproject 2 (Early Recognition) aimed to identify individuals at risk for schizophrenia and bipolar disorder. Additionally to psychopathology assessment, neuropsychological testing has been conducted to find cognitive dysfunctions in the at-risk individuals. Subproject 6 aimed to identify neurophysiological abnormalities, which can be used as potential biomarkers for the at-risk state of schizophrenia and bipolar disorder.

The studies presented in this work used the functional near-infrared spectroscopy (fNIRS) to measure the brain activation during two neuropsychological tasks. This method is particularly fitting for the early recognition research because it is relatively insensitive to movement and it is well suited for restless participants who may have problems during long monotonous

studies. Furthermore, it is inexpensive and easy to apply, which could facilitate investigating large study populations as well as transition to the clinical practice in the future.

The prefrontal cortex (PFC) has been chosen as the region of interest in both studies presented here. Previous research has reported cognitive deficits as well as related deficits in PFC functioning in manifest schizophrenia and bipolar patients. Study 1 assessed emotional interference measured by the emotional Stroop task, whereas Study 2 used a well-established semantic and phonemic verbal fluency task (VFT).

Both of these studies showed decreased performance and alteration in the PFC activation in the at-risk individuals compared to the healthy controls. The results of emotional Stoop task showed decreased performance and PFC activation in the individuals at risk for schizophrenia compared to the healthy controls. Furthermore, groups at risk for schizophrenia and bipolar disorder showed decreased activation in the frontotemporal cortex (FTC), which points to general deficits in processing of written language. During VFT, only the individuals at risk for schizophrenia showed decreased performance and decreased PFC activation compared to the healthy controls, which points to possibly deficient word retrieval strategies in individuals at risk for schizophrenia. Unexpectedly, individuals at risk for bipolar disorder showed increased PFC activation, which was significantly higher compared to participants at risk for schizophrenia. These results indicate neurophysiological differences in word retrieval between the two at-risk groups.

There is still a very long way to go until reliable biomarkers for early recognition of schizophrenia and bipolar disorder will be established. Even promising candidates do not show sufficient specificity, selectivity and predictive validity to be applied in clinical diagnostics. Therefore, large-scale longitudinal studies are needed. The studies presented in this dissertation showed that individuals at risk for schizophrenia and bipolar disorder differ in performance and frontal brain functioning not only from the healthy controls but also between each other. Nevertheless, these results are only preliminary. In the next steps it is essential to investigate whether the PFC activation during emotional Stroop and VFT is stable over time or changes with the progression to manifest disorders. Moreover, predictive validity of these activation abnormalities has to be assessed as individuals progress to manifest disorders.

Zusammenfassung

Die Früherkennung von Schizophrenie und bipolaren Störungen wurde in den letzten Jahren zu einem verbreiteten und wichtigen Forschungsthema. Obwohl die ersten Symptome dieser beiden Störungen schon in der Adoleszenz auftreten können, werden die Störungen selbst während der ersten Jahre danach häufig falsch oder gar nicht diagnostiziert. Es wurde gezeigt, dass eine Behandlungsverzögerung oder eine falsche Behandlung einen negativen Einfluss auf den Verlauf der Störung haben können. Aus diesem Grund versuchen einige Früherkennungsprogramme, die Risikoindividuen zu identifizieren, bevor die Störungen manifest werden.

Diese Programme basieren meistens auf der Beurteilung von verschiedenen psychopathologischen Symptomkonstellationen. Diese Symptome und andere Risikofaktoren sagen allerdings auch andere psychische Störungen vorher, was die Früherkennungsdiagnostik schwierig macht. Daher werden objektiv messbare biologische Marker gesucht, welche die Präsenz, die Absenz oder den Zustand einer Störung zeigen. Trotz intensiver Forschung wurden bisher keine Biomarker gefunden, welche genügend Sensitivität und Spezifizität aufweisen. Das Ziel dieser Dissertation war es, die frontale Hirnfunktionen in Individuen mit Risiko für Schizophrenie oder bipolare Störung zu untersuchen und dadurch zur Früherkennungsforschung beizutragen.

Die in dieser Dissertation verwendeten Daten wurden im Rahmen des Zürcher Impulsprogramms zur nachhaltigen Entwicklung der Psychiatrie (ZInEP), Teilprojekte 2 und 6, erhoben. Ziel des Teilprojekts 2 (Früherkennung) war es, Personen mit Risiko zu identifizieren, Schizophrenie oder eine bipolare Störung zu entwickeln. Zusätzlich zur psychopathologischen Diagnostik wurden neuropsychologische Tests durchgeführt um kognitive Auffälligkeiten der Risikopersonen zu finden. Ziel des Teilprojekts 6 war es, bei Risikopersonen neurophysiologische Auffälligkeiten den Risikopersonen zu identifizieren, welche als potenzielle Biomarker verwendet werden können.

Die in diesem Werk präsentierten Studien nutzen die funktionale nah-infrarot Spektroskopie (fNIRS), um die Hirnaktivität während zwei neuropsychologischen Aufgaben zu messen. Diese Methode ist für Früherkennungsstudien besonders gut geeignet: da es relativ bewegungsunempfindlich ist, eignet sich fNIRS für Personen, die Probleme haben während

langen, monotonen Untersuchungen ruhig zu bleiben. Zudem ist das Verfahren günstig und einfach anzuwenden, was sowohl für die Untersuchung grosser Populationen als auch künftige Anwendung in der klinischen Praxis relevant ist.

Der präfrontale Cortex (PFC) wurde in den beiden Studien als der Bereich von Interesse gewählt. Bisherige Forschung liefert Hinweise zu kognitiven Dysfunktionen und damit verbundenen Dysfunktionen bei der PFC-Aktivierung bei Patienten mit manifester Schizophrenie oder bipolarer Störung. Studie 1 hat die emotionale Interferenz mittels des emotionalen Stroop Tests untersucht. In Studie 2 wurde der gut etablierte semantische und phonemische Wortflüssigkeitstest (VFT) verwendet.

Beide Studien zeigten verminderte Leistung und Dysfunktionen bei der PFC-Aktivierung bei Risiko-Individuen im Vergleich zur Kontrollgruppe. Die Resultate des emotionalen Stroop Tests zeigten verminderte Leistung und PFC-Aktivierung in den Individuen mit dem Risiko, Schizophrenie zu entwickeln, im Vergleich zu der Kontrollgruppe. Weiterhin haben Individuen mit Risiko, Schizophrenie und bipolare Störung zu entwickeln, eine verminderte Aktivierung im frontotemporalen Cortex (FTC) gezeigt, was auf generelle Defizite in der Bearbeitung geschriebener Sprache hindeutet. Während dem VFT haben nur die Individuen mit Risiko, Schizophrenie zu entwickeln, verminderte Leistung und PFC-Aktivierung im Vergleich zur Kontrollgruppe gezeigt. Dies deutet darauf hin, dass diese zwei Gruppen wahrscheinlich unterschiedliche Strategien verwenden, um Wörter wiederzugeben. Unerwartet war, dass die Personen mit Risiko, eine bipolare Störung zu entwickeln, eine erhöhte PFC-Aktivierung gezeigt haben, die signifikant höher war als bei Individuen mit Risiko, Schizophrenie zu entwickeln. Diese Resultate weisen auf neurophysiologische Differenzen bei den Strategien zur Wörterwiedergabe zwischen den beiden Gruppen hin.

Es ist nach wie vor ein langer Weg, bis zuverlässige Biomarker für die Früherkennung von Schizophrenie und bipolaren Störungen etabliert werden. Auch die vielversprechenden Kandidaten zeigen ungenügende Spezifizität, Selektivität und prädiktive Validität, um für die Diagnostik angewendet zu werden. Die in dieser Dissertation präsentierten Studien haben gezeigt, dass Personen mit Risiko, Schizophrenie und bipolare Störung zu entwickeln, sich bezüglich der kognitiven Leistung und der frontalen Hirnfunktionen unterscheiden, und dies nicht nur von der Kontrollgruppe, sondern auch voneinander. Dies sind jedoch nur erste Vorergebnisse. In den nächsten Schritten ist es äussert wichtig zu untersuchen, ob die PFC-

Aktivierung während des emotionalen Stroop Tests und des VFT stabil bleibt oder sich mit dem Übergang zur manifesten Erkrankung verändert. Weiterhin muss die prädiktive Validität der Aktivierungsauffälligkeiten untersucht werden.

Abbreviations

ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APS	attenuated psychosis syndrome
ARMS	at-risk mental state
BIP	at risk for bipolar disorder
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BOLD	blood-oxygen-level dependent
BPSS-P	Bipolar Prodrome Symptom Interview and Scale-Prospective
BSABS	Bonn Scale for the Assessment of Basic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CBSI	correlation based signal improvement
COGDIS	cognitive disturbances
COPER	cognitive-perceptive (symptoms)
CW	continuous wave
DLPFC	dorsolateral prefrontal cortex
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DUP	duration of untreated psychosis
EEG	electroencephalography
ER	error rate
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
FTC	frontotemporal cortex
GAF	Global Assessment of Functioning
HAMD	Hamilton depression rating scale
HC	healthy controls
HCL	hypomania check list
HHb	deoxygenated hemoglobin
HR	high risk for schizophrenia
IQ	intelligence quotient
MINI	Mini-International Neuropsychiatric Interview

MPFC	medial prefrontal cortex
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest
O_2Hb	oxygenated hemoglobin
PANSS	Positive and Negative Syndrome Scale
PFC	prefrontal cortex
ROI	region of interest
RT	reaction time
SIPS	Structured Interview for Prodromal Symptoms
SOPS	Scale of Prodromal Symptoms
SPI	Schizophrenia Proneness Instrument
SPI-A	Schizophrenia Proneness Instrument, Adult version
SPI-CY	Schizophrenia Proneness Instrument, Child and Youth version
UHR	at ultra-high risk
VFT	verbal fluency test
WHO	World Health Organization
ZInEP	Zurich Program for Sustainable Development of Mental Health Services (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie)

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), schizophrenia and bipolar disorder belong to two different diagnostic groups: the first one to the schizophrenia spectrum and other psychotic disorders, and the second one to the bipolar and related disorders (American Psychiatric Association, 2013). However, in the clinical reality, the distinction between schizophrenia and bipolar is not entirely straightforward (Murray et al., 2004). Despite several differences, these mental disorders show some similarities in cognitive deficits and share some genetic predisposition (Krabbendam, Arts, van Os, & Aleman, 2005; Murray et al., 2004).

Schizophrenia is a severe and complex mental disorder. It is characterized by the presence of two or more of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms (American Psychiatric Association, 2013). The disorder is mostly diagnosed in late childhood or early adolescence (Kirkbride, Fearon, Morgan, & et al., 2006). However, the first, rather unspecific symptoms may emerge even several years earlier (Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010). The course of schizophrenia varies strongly between individuals, ranging from progressive improvement over time to chaotic and severe course (Newman, Bland, & Thompson, 2012). Nevertheless, it has been estimated that approximately 40% patients still show “intermediate” or “good” outcome (Menezes, Arenovich, & Zipursky, 2006).

With lifetime prevalence estimated at 1%, schizophrenia is not a common mental disorder, but it cannot be considered rare either (World Health Organisation, 2001). Furthermore, schizophrenia is one of the disorders having a very high burden on the affected individuals and their social environment (Jablensky, 2000; Magliano et al., 1998; Rössler, Joachim Salize, van Os, & Riecher-Rössler, 2005), as well as the highest economic impact (van Os & Kapur, 2009). Therefore, attempts have been made to identify and better understand genetic and environmental risk factors, as well as neurobiological and neuropsychological abnormalities (Frith, 1996; Woodward, 2014). Nevertheless, our understanding of schizophrenia is still insufficient (Tandon, Keshavan, & Nasrallah, 2008; van Os & Kapur, 2009).

Bipolar disorder is a severe mental illness with profound negative effects on social functioning of the affected individuals (Cannon et al., 1997; Lam & Wong, 1997). The two main disorders encompassed in the group "bipolar and related disorders" are bipolar I and bipolar II (American Psychiatric Association, 2013). Bipolar I is characterized by at least one manic episode. A major depressive episode is not a necessary diagnostic requirement. However, it often precedes or follows a manic episode (American Psychiatric Association, 2013). Bipolar II is diagnosed when at least one major depressive episode and at least one hypomanic episode have been reported (American Psychiatric Association, 2013).

According to the DSM-V, a manic episode is a period of time during which one's mood is persistently and abnormally elevated, and goal-directed activity or energy is increased. These symptoms have to last for at least a week (American Psychiatric Association, 2013). Furthermore, during this period the following symptoms (at least three) have to emerge: inflated self-esteem or grandiosity, decreased need for sleep, pressure to keep talking, racing thoughts or flight of ideas, distractibility, increased goal-directed activity or psychomotor agitation, and excessive involvement in activities with negative or painful consequences (American Psychiatric Association, 2013). A hypomanic episode is characterized by the same set of symptoms as a manic episode, but they only have to last at least four consecutive days. On the other end of the spectrum of the bipolar disorder lies the major depressive episode, which is diagnosed when depressed mood or loss of interest or pleasure and at least four additional symptoms are present for at least two weeks. The additional symptoms include: significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, and recurrent thoughts of death including suicide ideation and attempts (American Psychiatric Association, 2013).

Because the symptoms of bipolar disorder often overlap with symptoms of other mental illnesses, the diagnosis is very difficult (Bauer & Pfennig, 2005). The lifetime prevalence of bipolar disorder (both types I and II) has been estimated at 2.1% (Merikangas et al., 2011). However, some researchers suggest that approximately half of the patients diagnosed with unipolar depression may in fact suffer from bipolar II disorder (Angst et al., 2003).

Age of onset of bipolar disorder (both types I and II) is usually in the early adulthood (Kawa et al., 2005). However, younger age of onset is also observed and it has been associated with

worse outcome (Cate Carter, Mundo, Parikh, & Kennedy, 2003; Coryell, Fiedorowicz, Leon, Endicott, & Keller, 2013). Individuals diagnosed before the 18th year of age reported more suicidal ideations or attempts and showed increased rapid cycling between the manic/hypomanic and depressive episodes as well as longer manic/hypomanic and depressive phases (Cate Carter et al., 2003; Coryell et al., 2013).

Because of the difficult diagnostic procedures and relative poor understanding of the prodromal phase of schizophrenia and bipolar disorder, better comprehension of the early neuropsychological and neurophysiological changes is needed. This dissertation focuses on the frontal brain functioning in individuals at risk for schizophrenia and bipolar disorder. Previous studies have shown that patients diagnosed with manifest schizophrenia and bipolar disorder exhibit abnormalities in this brain region during various cognitive tasks (Barch, Carter, Braver, & et al., 2001; Brooks et al., 2015; Dell'Osso et al., 2015; William M. Perlstein, Carter, Noll, & Cohen, 2001). Moreover, alterations in behavior and brain functioning of at-risk individuals have been observed (Metzler et al., 2014). Investigating these alterations could increase our understanding of the neurological abnormalities in at-risk individuals before schizophrenia and bipolar disorder become fully manifest. Furthermore, the findings could be a base to improve the early recognition of these disorders.

The Zurich Program for Sustainable Development of Mental Health Services (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie, ZInEP) is a large-scale, multilevel research project conducted at the University Hospital of Psychiatry Zurich. The aim of the project is to bridge the gap between research and patient-care. ZInEP consistes of eight subprojects covering a bright spectrum from social psychiatric to neurophysiological aspects. The data presented in this dissertation were collected within the framework of the ZInEP subprojects 2 and 6. More information about ZInEP can be found under www.zinep.ch.

Subproject 2 (Early Recognition) (Theodoridou et al., 2014), led by Prof. Dr. med. Wulf Rössler, focused on identification of individuals at risk for schizophrenia and bipolar disorder. Several early recognition centers were set up in the Canton of Zurich. Individuals with first signs of mental decompensation, who contacted the centers, were offered a thorough medical and psychological assessment. Apart from established diagnostic interviews identifying the early psychopathological symptoms of schizophrenia and bipolar disorder,

neuropsychological, neuroanatomical, and neurophysiological (as a part of the subproject 6) parameters were assessed. The aim of the subproject was to identify abnormalities that are characteristic for schizophrenia and bipolar disorder and to establish potential biomarkers, which may be incorporated in the diagnostic procedures. The Early Recognition subproject also provided counseling and support for the affected individuals and family members.

Subproject 6, (Center for Neuro- and Sociophysiology (CNS)) was led by Prof. Dr. med Wolfram Kawohl and Dr. med. Helene Haker. The focus was to conduct neuro- and sociophysiological assessments of the participants recruited in the other ZInEP subprojects Early Recognition, Epidemiology and Supported Employment. The aim was to identify dysfunctions in brain functioning, which could be used as a potential biomarker, using electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS). Furthermore, other aspects, such as conscious social-cognitive abilities and involuntary social-physiological phenomena were investigated using a socio-physiological test battery. These parameters constitute complex interpersonal phenomena (e.g., empathy) and when impaired have a large impact on social functioning of an individual.

In the following chapter, the issue of early recognition of mental disorders, especially schizophrenia and bipolar disorder, is discussed (chapter 2.1). Furthermore, the current literature regarding frontal brain functioning in manifest schizophrenia and bipolar disorder patients is reviewed (chapter 2.2). The aims of the dissertation are presented in chapter 3. In the methodological section (chapter 4), the brain imaging method applied in the empirical studies (functional near-infrared spectroscopy), as well as the neuropsychological tasks employed in the empirical part, are discussed in detail. The empirical part (chapter 5) consists of two studies, which investigate prefrontal brain activity in individuals at risk for schizophrenia and bipolar disorder. In each study, a different neuropsychological task, requiring prefrontal brain activation, was used. Study 1 (chapter 5.1) employs an emotional Stroop paradigm and investigates interference of positively and negatively valenced emotional words on visual word processing. Study 2 (chapter 5.2) employs a well-known verbal fluency test (VFT), which investigates word-retrieval strategies (Troyer, Moscovitch, & Winocur, 1997). The empirical part is followed by a general discussion (chapter 6), presenting main conclusions from both studies. Furthermore, main limitations and directions for future research are debated.

2. Theoretical background

2.1 Early recognition of mental disorders

First symptoms of many psychiatric disorders often emerge in adolescence or early adulthood, but the disorders are diagnosed up to several years later (Alfredo Carlo Altamura, Buoli, Albano, & Dell'Osso, 2010; A. C. Altamura, Dell'Osso, Mundo, & Dell'Osso, 2007; Fusar-Poli, Borgwardt, Bechdolf, & et al., 2013; Hauser et al., 2007; Mandell, Novak, & Zubritsky, 2005). This delay between appearance of the first symptoms and treatment might have a negative influence on course of the disorder, social environment, and even life expectancy of the affected individuals (Berk & Dodd, 2005; Marshall et al., 2005; Mossaheb, Wiesegger, Amminger, Kasper, & Tauscher, 2006; Perkins, Gu, Boteva, & Lieberman, 2005). Therefore, early recognition of mental disorders is a vital field of psychiatric research. Furthermore, the importance of early recognition has been recognized by the World Health Organization (WHO), who proposed it as a possible method of prevention of mental disorders (World Health Organization, 2004).

There are several clinical tools focusing on the assessment of early symptoms of mental disorders, for example Structural Interview for Prodromal Symptoms (SIPS, McGlashan, Miller, Woods, Hoffman & Davidson, 2001) or Bipolar Prodrome Symptom Interview and Scale – Prospective (BPSS-P, Correll et al., 2014). However, in earlier stages of mental disorders, the clinical symptoms are mostly unspecific forcing a compromise between specificity and detection rate of the available diagnostic tools (Bender, Weisbrod, & Resch, 2007). Therefore, attempts have been made to supplement the clinical instruments with more specific neuropsychological, electrophysiological and neuroimaging examinations (Bender et al., 2007). This led to a search for specific endophenotypes and biological markers, which reflect the genetic vulnerability, accumulation of stress factors, and interaction of these (Bender et al., 2007).

Endophenotypes are physiological markers that reflect underlying genetic vulnerability (Braff, Freedman, Schork, & Gottesman, 2007). They can be reliably measured and potentially used in diagnostic procedures, as in case of juvenile myoclonic epilepsy endophenotype (Greenberg, Delgado-Escueta, Maldonado, et al., 1988; Greenberg, Delgado-Escueta, Widelitz, et al., 1988; Greenberg et al., 2000). Creating a link between genetics and behavioral symptoms, endophenotypes are trait-markers, meaning they can be observed

independent of the manifestation of a mental disorder (Bender et al., 2007). Therefore, an endophenotype could indicate which individuals are at risk of developing a particular disorder before its manifestation (Cadenhead, 2002).

Biological markers compose a broader category of genetically and environmentally determined parameters, which can be applied in diagnostic procedures (Bender et al., 2007). They could be either trait-markers or state-markers, present only during particular stages of a disorder (e.g., shortly before acute psychosis) (Bender et al., 2007). However, reliable biological state-dependent markers are not easy to identify.

Research aiming to identify diagnostically relevant endophenotypes and biological markers is ongoing. However, no neurobiological parameters have been accepted as diagnostic tools (American Psychiatric Association, 2013; Hyman, 2007). The most promising future approach for early recognition of mental disorders should focus in the first line on the assessment of early psychiatric symptoms, but also be supplemented by a combination of state and trait-markers.

2.1.1 Early recognition of schizophrenia

For the past two decades, research investigating early recognition of mental disorders focused especially on schizophrenia. Development of various criteria for the "at-risk mental state" (ARMS) is partially reflected in the creation of a new category in the DMS-V – attenuated psychosis syndrome (American Psychiatric Association, 2013). This category includes the individuals with mild psychotic-like symptoms, which would not meet the diagnostic criteria for other disorders. Previous research has shown that many of these individuals might develop a psychotic disorder (Carpenter & van Os, 2011). However, the attenuated psychosis syndrome can be related to several potential outcomes, only one of them being a transition to manifest schizophrenia (Fusar-Poli et al., 2013). Several studies have shown that the delayed treatment and longer duration of the untreated psychosis (DUP) associate negatively with individual's prognosis (Mossaheb et al., 2006). Therefore, better early recognition strategies may improve the prognosis and may be implemented as potential mechanism to prevent negative outcome (Birchwood & Macmillan, 1993).

In the early at-risk state of psychosis, the so-called basic symptoms emerge. These symptoms are distinct from the classic psychotic symptoms and involve disturbances in the cognitive

domains of perception, thought processing, language, and attention (Fusar-Poli et al., 2013). These early deficits can be grouped into two categories: cognitive-perceptive symptoms (COPER; e.g., derealisation and visual or acoustic disturbances) and cognitive disturbances (COGDIS; e.g., inability to divide attention, disturbances of abstract thinking, and disturbances of expressive speech). The second category encompasses most of the predictive basic symptoms for the transition to manifest psychosis (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer, & Ruhrmann, 2007).

As the prodromal phase of schizophrenia progresses more psychotic symptoms emerge. Klosterkötter, Hellmich, Steinmeyer, and Schultze-Lutter (2001) described and summarized these symptoms in the ultra-high-risk criteria. They include attenuated psychotic symptoms (APS; e.g., perceptual abnormalities, odd thinking and speech, and paranoid ideation), brief limited intermittent psychotic episode (BLIP; e.g., hallucinations, delusions, and formal thought disorder), and a family history of psychosis or schizotypal personality combined with at least 30% decrease in global assessment of functioning in the past year (Fusar-Poli et al., 2013).

The progression of symptoms and transition to manifest psychosis are depicted in Figure 1. Even though basic symptoms may appear earlier than the APS and BLIP, they present a set of complementary features and not distinct stages. Therefore, clinical assessment of both types of symptoms simultaneously should be considered (Fusar-Poli et al., 2013; Fusar-Poli, Borgwardt, & Valmaggia, 2008).

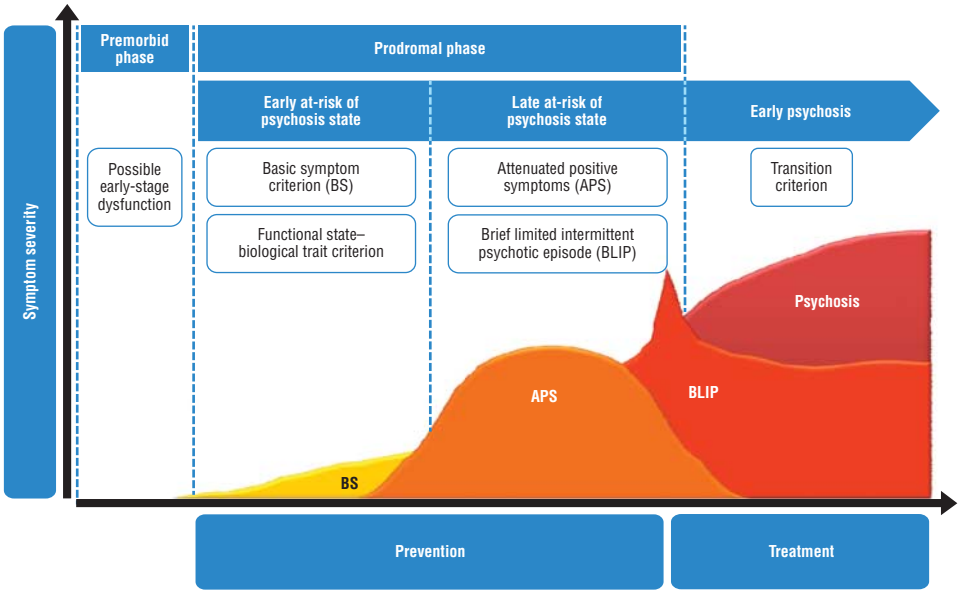

Figure 1. Symptoms progression in the prodromal phase to manifest psychosis (from Fusar-Poli et al., 2013).

Several diagnostic instruments are currently being used to assess the basic symptoms, for example the Bonn Scale for the Assessment of the Basic Symptoms (BSABS, Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001) or Schizophrenia Proneness Instrument (SPI), which is available as adult (SPI-A, Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007) and child and youth version (SPI-CY, Schultze-Lutter & Koch, 2010) . The most common interview instruments used for the assessment of the ultra-high-risk criteria are the Comprehensive Assessment of the At-Risk Mental State (CAARMS, Young et al., 2005) and Structured Interview for Prodromal Symptoms (SIPS), including the companion Scale of Prodromal Symptoms (SOPS) (T. J. Miller et al., 2003). However, even these established instruments are not fully satisfactory, as patients showing mostly early negative symptoms remain under-detected (Bender et al., 2007; Galderisi et al., 2002). To improve the diagnostic procedures many studies have been investigating possible genetic markers and endophenotypes (Lee et al., 2012; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Turetsky et al., 2007).

2.1.2 Early recognition of bipolar disorder

Early recognition of bipolar disorders is a hot topic in psychiatric research. In their review, Hauser et al. (2007) recognized the urgent need for the timely recognition of early stages of

bipolar disorder. However, the first interview assessing the prodromal bipolar symptoms has been validated only recently (Correll et al., 2014).

Similarly to schizophrenia, bipolar disorder is also often diagnosed several years after onset (Hauser et al., 2007, see Figure 2). Patients often receive wrong diagnoses at first, which might range from depression to attention-deficit hyperactivity disorder (ADHD) or schizophrenia. Depression is a very common misdiagnosis of bipolar disorder, as many patients seek help only during depressive episodes (Hauser et al., 2007). It has been shown that an inappropriate treatment, caused by a misdiagnosis, may have negative consequences on the course of the disorder (Hauser et al., 2007). For example, use of antidepressants in case of a bipolar disorder may lead to strong mood swings and trigger manic symptoms (Ghaemi, Hsu, Soldani, & Goodwin, 2003; Reichart & Nolen, 2004).

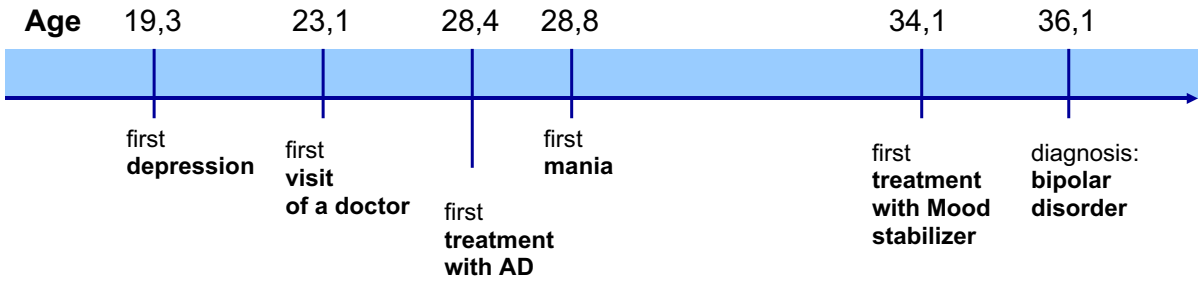

Figure 2. Time axis showing the delayed diagnosis of bipolar disorder (from Hauser et al., 2007).

Currently, only one comprehensive interview assessing the prodromal symptoms, the Bipolar Prodrome Symptom Interview and Scale–Prospective (BPSS-P), has been validated in psychiatric patients and healthy individuals (Correll et al., 2014). Nevertheless, its predictive validity still remains to be assessed. Many studies investigating individuals at risk for bipolar disorder have used family history of bipolar disorder (diagnosed parent or sibling) as the criterion to identify high-risk individuals (Brotman et al., 2008; Miklowitz et al., 2013; Sprooten et al., 2011). Several studies identified further risk factors and psychiatric symptoms to be predictive for bipolar disorder, which included: affective liability, irritability, impulsivity, anger, depression, anxiety, substance use disorder, sleep disorders and disturbances in attention and cognition (Brietzke et al., 2012; Faedda et al., 2014). However, these factors are also good predictors of other psychiatric disorders. Therefore, combining these with family history of bipolar disorder could possibly yield a good predictive model (Faedda et al., 2014). Nevertheless, multifactorial models, including genetic, biological and environmental markers, still need to be developed and validated (Brietzke et al., 2012).

2.2 Prefrontal cortex

The frontal lobe accounts for approximately one third of the human brain. It can be considered one of the most important structures as it represents all functional parts of the cortex (Mesulam, 2002). The prefrontal cortex (PFC) is a part of the frontal lobe including Brodmann areas 9, 10, 11, 12, 46, and 47 (Brodmann, 1909). It represents a complex cytoarchitecture and connectivity (Rajkowska & Goldman-Rakic, 1995a, 1995b), and multiple neurotransmitters such as dopamine, norepinephrine, serotonin and acetylcholine, play a role in it's functioning (Arnsten & Robbins, 2002).

In all its complexity, the PFC requires sufficient time to develop and mature. Studies have shown that the development of the PFC begins already in early childhood and lasts till early adulthood (Gogtay et al., 2004; Tsujimoto, 2008). In the early age, on the neuronal level the synaptic density decreases, whereas increase in gray and white matters and myelination have been observed (Tsujimoto, 2008). A prospective longitudinal study by Gogtay et al. (2004) described development of the human brain from childhood to adolescence and showed that the prefrontal cortex was the last brain region to fully mature. Maturation of the PFC is also visible on the cognitive level as the abilities associated with more efficient processing and better performance become visible (Tsujimoto, 2008).

The PFC is not responsible for storing or processing any particular information. However, it interacts with other brain regions and many cognitive processes are influenced by the PFC (Picton, Alain, & McIntosh, 2002). These include working memory, selective attention, inhibitory functions (Braver, Cohen, & Barch, 2002) and many others (for a comprehensive review, see E. K. Miller & Cohen, 2001; Stuss & Knight, 2002). Dysfunctions in the PFC functioning are reflected in abnormalities of various cognitive domains. These abnormalities are an integral part of psychopathology of several mental disorders such as: attention deficit hyperactivity disorder, major depression, various psychotic disorders, as well as schizophrenia and bipolar disorder (for example: Callicott et al., 2003; Clark, Iversen, & Goodwin, 2001, 2002; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Slifstein, van de Giessen, Van Snellenberg, & et al., 2015).

2.2.1 Prefrontal cortex deficits in schizophrenia

PFC dysfunctions are commonly found in manifest schizophrenia patients. A decreased activity of the PFC has been first described by Ingvar and Franzen (1974) and named the

"hypofrontality". Since then, hypofrontality has been widely reported in studies applying various neurophysiological and imaging methods (Andreasen, Rezai, Alliger, & et al., 1992; Ehlis, Herrmann, Plichta, & Fallgatter, 2007; Ehlis et al., 2011; Fallgatter & Müller, 2001). All these PFC dysfunctions are reflected in related cognitive deficits such as working memory (Carter et al., 1998), inhibition of motor responses (Fallgatter & Müller, 2001), and inhibition of competing information (Ungar, Nestor, Niznikiewicz, Wible, & Kubicki, 2010).

Electroencephalography (EEG) studies have described hypofrontality as a slowing of the EEG activity observed in the frontal electrodes (Coger, Dymond, & Serafetinides, 1979; Guich et al., 1989). Furthermore, studies investigating event related potentials described decreased or shifted prefrontal response (Fallgatter & Müller, 2001). Other imaging studies have reported decreased activation in PFC during working memory and selective attention tasks as well as during a logical thinking Tower of London task (Andreasen et al., 1992; Barch et al., 2001; Ungar et al., 2010). Moreover, aberrant resting-state connectivity in the PFC adds to the list of the dysfunctions (Chai et al., 2011; Zhou et al., 2007).

Nevertheless, hypofrontality is not the only PFC dysfunction observed in manifest schizophrenia patients. An opposite effect, that is, increased PFC activity, has also been described (Manoach, 2003; Soyka, Koch, Möller, Rüther, & Tatsch, 2005). In a comprehensive review, Manoach (2003) made an attempt to understand the underlying causes of these two seemingly paradoxical phenomena. She concluded that the heterogeneity of results might be caused by methodological issues such as the exact task specification, medication effects or heterogeneous patients groups. However, it might also be explained be a fundamental feature of schizophrenia, as patients often show increased variability and decreased stability of the results compared to healthy controls (Manoach, 2003).

The increasing amount of studies showing hypofrontality in manifest schizophrenia patients led to investigation of the PFC dysfunctions in individuals at risk for this disorder. Neuropsychological tests have shown decreased performance in first-degree relatives of schizophrenia patients, especially during working memory tasks (e.g., Toomey et al., 1998) . However, imaging studies have delivered some inconsistent results. Walton et al. (2014) reported an association between a polygenetic risk for schizophrenia with PFC inefficiency during a working memory task. However, other studies have reported increased PFC activation in at-risk individuals during the n-back working memory, even though the at-risk

groups and the control group did not differ in the performance task (Callicott et al., 2003; Falkenberg et al., 2015).

2.2.2 Prefrontal cortex deficits in bipolar disorder

Similarly to schizophrenia patients, bipolar disorder patients also show cognitive and executive deficits, which indicate some PFC abnormalities (Robinson et al., 2006). Neuropsychological studies have reported deficits in various executive functions, with the phenotype often being an intermediate one between schizophrenia patients and healthy individuals (Krabbendam et al., 2005; Zalla et al., 2004). Furthermore, it has been shown that strength of the executive dysfunctions in bipolar patients correlates positively with the number of depressive and manic episodes (Zubieta, Huguelet, O'Neil, & Giordani, 2001)

Surprisingly, there are relatively few imaging studies investigating the PFC dysfunctions in patients with bipolar disorder and the results are somewhat inconsistent. It is possible that the inconsistencies are caused by very heterogeneous patients samples. Brooks et al. (2015) observed PFC hypoactivation during working memory task in bipolar II depressed patients. However, Dell'Osso et al. (2015) reported increased PFC activation in euthymic bipolar I and bipolar II patients. Furthermore, during a selective attention task, decreased PFC activation has been described in stable and remitted patients (Gruber, Rogowska, & Yurgelun-Todd, 2004; Kronhaus et al., 2006). In a resting-state connectivity study, Anticevic et al. (2013) reported a decreased connectivity between medial PFC and amygdala, which points to a deficient emotion regulation.

3. Aims of the dissertation

The overall aim of this dissertation was to investigate the prefrontal brain activity in individuals at risk for schizophrenia and bipolar disorder. We expect that, in the future, PFC alterations might be used as biological markers in early recognition of these disorders. The focus of the work presented here lies not only on finding differences between individuals at risk for the two mental disorders and healthy persons, but also on finding differences between the at-risk stage for schizophrenia and bipolar disorder.

Numerous studies have shown that the cognitive and neuropsychological deficits can be observed as early as the at-risk stage and remain stable throughout the course of the disorder (Becker et al., 2010; Metzler et al., 2015). In the current work, we investigated the prefrontal cortex (PFC) functioning, as dysfunctions in this particular brain area have been reported in several psychiatric disorders including schizophrenia and bipolar disorder (Clark, Iversen, & Goodwin, 2001; Dell'Osso et al., 2015; Manoach, 2003; Wuebben & Winterer, 2001). The two tasks presented in this dissertation are the emotional Stroop task (Study 1) and the verbal fluency task (Study 2), which are well established and have been widely described in literature (Dieler, Tupak, & Fallgatter, 2012; J. M. G. Williams, Mathews, & MacLeod, 1996; J. M. G. Williams & Nulty, 1986). Previous research has shown involvement of the PFC during both tasks in healthy individuals (Tupak et al., 2012; Tupak et al., 2013). Furthermore, deficits in performance and PFC dysfunctions during these have been observed in psychiatric patients (Dieler et al., 2012; Dresler et al., 2012; J. M. G. Williams et al., 1996).

Study 1 focused on the emotional interference and related PFC activity. Emotional interference, observed as longer reaction times for naming the font color of emotionally valenced than neutral words, has been well described in healthy individuals and various psychiatric patients (J. M. G. Williams et al., 1996). Moreover, according to previous research, anxiety prone individuals have shown longer reaction times and decreased dorsolateral prefrontal cortex (DLPFC) activation compared to less anxiety prone individuals (Tupak et al., 2013). Since anxiety is one of the symptoms of the prodromal phase (Yung & McGorry, 1996a, 1996b), we expected to observe lower reaction times and lower DLPFC activation in the individuals at risk for schizophrenia than in the healthy controls. Furthermore, anxiety is also a common comorbid symptom of bipolar disorder (Simon et al.,

2004). Therefore, we expected to observe similar results for the individuals at risk for this disorder.

Study 2 investigated prefrontal brain activation during the semantic and phonemic verbal fluency task (VFT). The two VFTs require different word-retrieval strategies and previous studies have shown that these are characterized by different brain activation patterms (Troyer et al., 1997; Tupak et al., 2012). During the phonemic VFT, the word retrieval strategies focus on the first phoneme of the word, which is considered more difficult than focusing on the semantic representations in the semantic VFT. Consequently, the phonemic VFT showed stronger performance differences between manifest schizophrenia and bipolar patients, and healthy individuals in previous research (Dieler et al., 2012). Furthermore, these results were mirrored by larger differences in PFC activation between manifest patients and healthy individuals (Dieler et al., 2012; Ehlis et al., 2007). Nevertheless, previous research comparing PFC activation between manifest schizophrenia and bipolar patients revealed rather inconsistent results (Dieler et al., 2012). Therefore, no hypotheses regarding the differences in brain activation between these at-risk groups were stated. However, we speculated that the VFT could help in differentiating between these groups.

4. Methods

4.1 Functional near-infrared spectroscopy (fNIRS)

The first application of the near-infrared technology to measure activity of the human brain has been described by Jobsis (1977). Since then the functional near-infrared spectroscopy (fNIRS) has gained popularity and has been widely used in neuropsychological and psychiatric research (Ehlis, Schneider, Dresler, & Fallgatter, 2014). fNIRS presents several advantages for this type of studies. Firstly, it is relatively insensitive to movement, allowing to investigate restless individuals and those who cannot keep still during long experimental procedures such as infants or attention deficit hyperactivity disorder patients (Ehlis, Bähne, Jacob, Herrmann, & Fallgatter, 2008; Inoue et al., 2012; Quaresima, Bisconti, & Ferrari, 2012). Secondly, it is a non-invasive and easy to apply method, which makes it particularly suitable for individuals who may have problems during other imaging procedures (e.g., are afraid of tight surroundings or have metal implants, such as pace maker or a cochlear implant). Thirdly, fNIRS can be well combined with other neurophysiological and neuroimaging methods, contributing to a better understanding of physiological and pathological neurological processes (Fazli et al., 2012; Okamoto et al., 2004; Roche-Labarbe, Wallois, Ponchel, Kongolo, & Grebe, 2007; Steinbrink et al., 2006; Wallois, Mahmoudzadeh, Patil, & Grebe, 2012).

Nevertheless, fNIRS is only able to measure the brain activity on the cortex surface, which is its major limitation. Furthermore, the time resolution of fNIRS is similar to the one found in fMRI. However, multimodal applications including fNIRS and EEG techniques increase the time resolution (Fazli et al., 2012; Roche-Labarbe et al., 2007; Wallois et al., 2012).

4.1.1 Functional basis of fNIRS

fNIRS allows to measure relative changes in concentrations of oxygenated and deoxygenated hemoglobin (O_2Hb and HHb respectively). Neurovascular coupling is the underlying principle of fNIRS and it is the same principle that underlies interpretation of the fMRI BOLD signal (Logothetis & Wandell, 2004). Therefore, studies comparing these two methods have delivered moderate to strong reliability indices (Plichta, Herrmann, Baehne, et al., 2006; Plichta, Herrmann, et al., 2007; Plichta, Herrmann, Ehlis, et al., 2006). Neurovascular coupling postulates that in the active brain regions O_2Hb concentration increases and HHb

decreases. An example of the hemodynamic response measured by fNIRS is depicted in Figure 3.

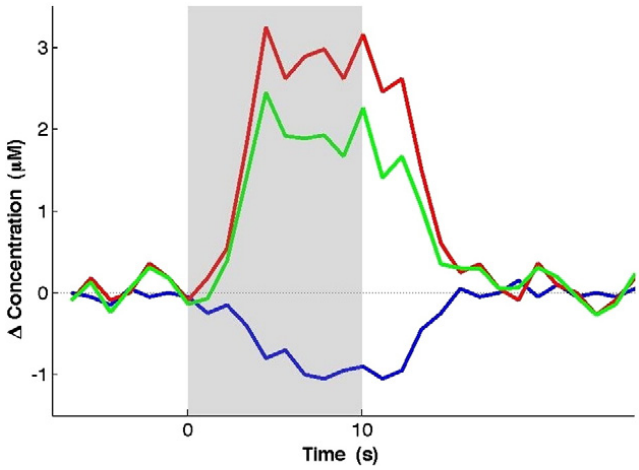

Figure 3. Example of a hemodynamic response measured by a single fNIRS channel. Relative changes in oxygenated hemoglobin (O_2Hb) are depicted in red, changes in deoxygenated hemoglobin (HHb) in blue and changes of the total hemoglobin in green. The gray rectangle shows the stimulation period. From Ferrari and Quaresima (2012).

In the continuous wave (CW) fNIRS, the emitters located on a scalp send out a constant beam of light from the near infrared spectrum in two separate wavelengths between 700 and 1000nm. The light passes through the tissue but is partially absorbed by O_2Hb and HHb (Obrig & Villringer, 2003; Simonson & Piantadosi, 1996). The unabsorbed light diffuses through the head tissues and can be measured by the fNIRS detectors (Ferrari, Mottola, & Quaresima, 2004). A simplified path of the near-infrared light is depicted in Figure 4.

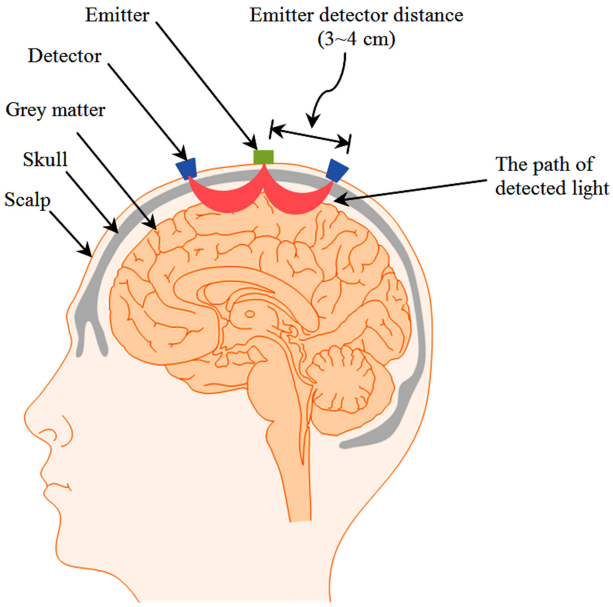

Figure 4. Acquisition of fNIRS signal. Example of the banana-shaped paths of light between the emitter and detectors. From Naseer and Hong (2015).

The distance between the light emitter and detector is of a great importance for fNIRS measurements. If the distances are too big (more than 5cm), the signal is weak and unstable, whereas if the distances are too small (less than 1cm), the light scattering will be measured mostly in the skin-level (Gratton et al., 2006). Therefore, the distance between 3 and 4 cm has been deemed optimal (Gagnon, Yücel, et al., 2012) and most commercial devices use the distance of 3cm (e.g., ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). Nevertheless, new methods, which use multiple emitter-detector distances, are being developed. The use of multiple distances (3cm as well as shorter and longer ones simultaneously) is very helpful to remove superficial signal contamination and increase image quality (Gagnon, Cooper, et al., 2012; Gagnon, Yücel, Boas, & Cooper, 2014)

4.2 Cognitive tasks

4.2.1 Emotional Stroop task

The task used in the first study was the emotional Stroop task, which is a version of a classical color-word Stroop. During this task, the participants are being shown emotionally valenced and neutral words and are asked to name as fast as possible the color of the font the word is written in.

This task is said to measure the emotional interference. Emotional valence of a word influences the visual processing of the colorful font and increases the reaction times (J. M. G. Williams & Nulty, 1986). On a behavioral level, many studies have shown increased reaction times in emotional Stroop in healthy individuals and various patient groups (J. M. G. Williams et al., 1996). Despite numerous behavioral studies, the imaging research is not well represented. Most studies with anxiety prone healthy individuals or anxiety patients have shown involvement of the dorsolateral and medial prefrontal cortex (DLPFC and MPFC), which was especially prominent for the negatively valenced words (Dresler et al., 2012; Tupak et al., 2013). Therefore, these regions were chosen as the regions of interest in the Study 1.

In the task employed in Study 1, 10 positively valenced, 10 negatively valenced, and 10 neutral words were shown in yellow, red, green and blue on a computer screen. The emotional Stroop was conducted as an event related design task. The inter-stimulus-interval was set at random between 4 and 8 seconds. These short intervals do not allow for the hemodynamic changes to return to the baseline state. Therefore, a model-based analysis was applied (Plichta, Heinzel, Ehlis, Pauli, & Fallgatter, 2007). It has been shown that similarly to fMRI event-related tasks, a general linear model approach can identify brain activation in tasks with inter-stimulus intervals between 4 and 9 seconds (Plichta, Heinzel, et al., 2007).

4.2.2 Verbal fluency test

Verbal fluency test (VFT) was the task used in Study 2. It is a well-established task, which was often used in fNIRS studies both with healthy individuals and various psychiatric patients (Dieler et al., 2012). This task emphasizes the insensitivity to movement as one of the main advantages of fNIRS. Using fNIRS, it is possible to record simultaneously behavioral and brain activation data, whereas fMRI only allows covert VFT (e.g., Weiss et al., 2004, Weiss et al., 2003).

In the current work, both semantic and phonemic VFT were employed. During the semantic VFT, individuals were asked to name as many nouns as possible belonging to a certain category, whereas during the phonemic VFT, they were asked to name as many nouns starting with a given letter. These two types of VFT are thought to employ different word-retrieval strategies and activate different brain structures (Tupak et al., 2012). Based on the previous research with healthy individuals and schizophrenia and bipolar disorder patients (Dieler et

al., 2012; Ehlis et al., 2007), PFC was the primary focus and the region of interests in our analysis.

Since word-production over time requires constant brain activation, VFT was a block design task with 30 second-long blocks of activation and 30 second-long breaks. In the analysis, the respective blocks were averaged yielding average changes in O_2Hb and HHb concentrations over the time. Relative changes in the hemoglobin concentration reach their peak approximately 4-6 seconds after beginning of stimulation and progressively decrease to the baseline level after the stimulation has finished (for an example see Figure 3). In the statistical analysis, the hemoglobin values were averaged over the maximal activation time (5-30 seconds after the start of a task) to obtain a single value for the brain activation in each channel.

5. Empirical part

5.1 Study I: Emotional Stroop task

Title

Frontal brain activity in individuals at risk for schizophrenia and bipolar disorder during the emotional Stroop task – An fNIRS study

Authors

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5.1.1 Abstract

Objectives

Despite the emotional Stroop effect being widely reported in the literature, only a few studies have inspected the underlying brain activity. The goal was to investigate the frontal brain activation in individuals at risk for schizophrenia and bipolar disorder during an emotional Stroop task.

Methods

Individuals at high risk for schizophrenia (HR), at ultra-high risk for schizophrenia (UHR), at risk for bipolar disorder (BIP) and healthy controls (HC) performed an emotional Stroop task, which included positively, negatively and neutrally valenced words. Functional near-infrared spectroscopy (fNIRS) was used to measure levels of oxygenated hemoglobin (O_2Hb) representing brain activity.

Results

Results showed decreased levels of O_2Hb in the bilateral dorsolateral prefrontal cortex (DLPFC) in the HR and UHR groups compared to the HC, indicating lower activity. Moreover, significantly lower O_2Hb levels in the frontotemporal cortex (FTC) were observed in all at risk groups compared to the HC.

Conclusions

Lower activity in the FTC in schizophrenia and bipolar at-risk groups reflects disorder unspecific dysfunctions. Decreased activity in the DLPFC in the HR and UHR groups indicates that hypofrontality can be found already in individuals at risk for schizophrenic psychosis. The most prominent in response to negative words might reflect increased fear sensitivity.

Key words: early recognition, at-risk stage, dorsolateral prefrontal cortex (DLPFC), emotion processing, emotional interference

5.1.2 Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging method, which is constantly gaining popularity in psychiatric research (Ehlis et al., 2014). It uses light from the near-infrared spectrum to measure relative concentrations of both oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin representing brain activity (Hoshi, 2003; Obrig & Villringer, 2003). The time course and shape of the hemodynamic response measured by fNIRS is comparable to the blood oxygenation level-dependent (BOLD) signal of functional magnetic resonance imaging (fMRI) (Logothetis & Wandell, 2004). fNIRS possesses many advantages. Unlike the other imaging methods fNIRS is easy to apply and does not require use of radioactive tracers. Furthermore, it is quite insensitive to movement, which often makes it very suitable for studies with psychiatric or nervous patients (e.g., Thome et al., 2012) . However, contrary to fMRI, the spatial resolution of fNIRS is rather low (~30 mm), limiting the measurement only to cortical activity.

Schizophrenia and bipolar disorder often start in adolescence or early adulthood but remain undiagnosed for an extended period of time (Angst et al., 2005; Beiser, Erickson, Fleming, & Iacono, 1993; Drancourt et al., 2013; Schimmelmann et al., 2008). It has been shown that a delay of diagnosis has a negative influence on the progression of the disorder, whereas an early and appropriate treatment has beneficial effects (Cadenhead, Light, Shafer, & Braff, 2005; Penttila, Jaaskelainen, Hirvonen, Isohanni, & Miettunen, 2014; Schimmelmann et al., 2008). Therefore, extensive research to identify individuals at risk for schizophrenia and bipolar disorder has been conducted (Angst et al., 2005; Fusar-Poli et al., 2013; Metzler et al., 2014). Furthermore, biological markers linking neurophysiological and behavioral symptoms of psychosis have been explored (Bender et al., 2007; Ehlis et al., 2011; Ferrarelli, 2013; Fusar-Poli, Smieskova, Serafini, Politi, & Borgwardt, 2012; Stöber et al., 2009). The goal of this study is to investigate differences in frontal brain activity in individuals at risk for schizophrenia and bipolar disorder during an emotional Stroop task.

The emotional Stroop task is a modification of the classic Stroop task, assessing the impact of emotional stimuli on attentional processes (J. M. G. Williams et al., 1996). During the task individuals are asked to name the ink color of emotionally valenced and neutral words (see Fig. 1). The emotional Stroop effect is a difference between the mean response time to the emotional and neutral words, thus indicating the so-called emotional interference. A stable emotional Stroop effect has been observed in anxiety patients and healthy, but anxious

individuals (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). Furthermore, the emotional Stroop effect has been observed in other psychiatric patient groups, when negative words related to their specific symptoms were used (J. M. G. Williams et al., 1996).

Emotional interference studies with schizophrenia patients showed rather heterogeneous results. In an emotional Stroop study, Demily et al. (2010) showed no difference in reaction times between schizophrenia patients and healthy individuals for negatively and positively valenced words (e.g. slaughter, failure and holidays, success). Contrary to these findings other studies showed a connection between the emotional interference and symptom-specific words. Besnier et al. (2011) reported increased emotional interference in schizophrenia patients, which also correlated with positive symptoms. However, negatively valenced, emotional words used in this study were related to paranoid symptoms (e.g. mad, invaded), and substantially differed from the negatively valenced words used by Demily et al. (2010). Nonetheless, also negative, anxiety-related words (e.g. panic, fearful) seem to have an influence on the emotional processing of individuals suffering from psychosis. Fear and Healy (1996) assessed emotional interference in delusional disorder patients elicited by words related to depression, threat and anxiety and reported significantly reduced interference in individuals on antipsychotic medication compared to medication naive ones. Only a few studies have investigated the emotional Stroop effect in bipolar patients. Still, the interference caused by depression and mania related words (e.g. sad, depressed or happy, agitation) has been observed in manic bipolar patients and their relatives (Besnier et al., 2011; Besnier et al., 2009).

Despite numerous studies investigating the emotional Stroop effect, only a few assess the related brain activity. Most of these studies used the fMRI technique. In healthy subjects Compton et al. (2003) discovered an increase of activity in dorsolateral prefrontal cortex (DLPFC), frontal cortex dorsal to ACC, orbitofronal cortex, bilateral inferior parietal lobes and bilateral superior temporal gyri as a response to color naming of the negative words compared to the neutral words. Furthermore, in an fNIRS study Tupak et al. (2013) showed decreased levels of oxygenated hemoglobin (O_2Hb) in DLPFC and MPFC in healthy individuals carrying a T allele of the neuropeptide S gene. These individuals seem to be more panic prone and therefore, the obtained results are said to reflect a less efficient prefrontal regulation system. Nevertheless, a recently done fMRI study reported contradictory results –

increased BOLD signal in the left inferior frontal gyrus as a response to panic related words in panic disorder patients (Dresler et al., 2012).

Until now, not many studies have investigated the emotional Stroop effect in patients with manifest schizophrenia and bipolar disorder (Besnier et al., 2011; Demily et al., 2010; Fear & Healy, 1996). In the study presented here, we want to investigate whether changes in attention, dorsolateral prefrontal and frontotemporal brain activity can be observed in individuals at-risk for these disorders, before the manifest symptoms appear. Based on the previous behavioral studies (e.g. Besnier, et al., 2011; Fear and Healy, 1996) and imaging findings (e.g. Tupak, et al., 2013) we hypothesized that the groups at risk for schizophrenia and bipolar disorder will show a lower DLPFC activity compared to healthy controls. Since previous studies have reported the strongest emotional interference for the negatively valenced words, the difference should be especially prominent in this category. Furthermore, it has been reported that patients with schizophrenia show poorer reading abilities (Zammit, Allebeck, David, & et al., 2004). Therefore, we additionally analyzed activity in the bilateral frontotemporal cortex, as this structure is responsible for recognizing visual objects and reading (Turkeltaub, Eden, Jones, & Zeffiro, 2002). We expected to see significantly lower frontotemporal activity reflected in smaller O_2Hb measures in the individuals at-risk for schizophrenia.

5.1.3 Materials and methods

Participants

169 participants between 13 and 35 years of age were recruited from individuals, who contacted any of the four Early Recognition Centers in the Canton of Zurich, Switzerland. The current study was a part of a prospective longitudinal study on early recognition of psychoses, which was a part of the "Zurich Program for Sustainable Development of Mental Health Services" (ZInEP, Zürcher Impulsprogram zur Entwicklung der Psychiatrie) The full study design is described elsewhere (Theodoridou et al., 2014).

The participants were assigned to one of four groups – at high risk for psychosis (HR), at ultra high risk for psychosis (UHR), at risk for bipolar disorder (BIP) and to a healthy control group (HC). This was based on the following inclusion criteria. The participants were included in the HR group if they experienced at least one cognitive-perceptive (COPER) basic symptom or at least two cognitive disturbances (COGDIS) assessed with the adult or

children-youth versions of the Schizophrenia Proneness Interview (SPI-A; Schultze-Lutter, et al., 2007, SPI-CY; Schultze-Lutter and Koch, 2010) . The inclusion criteria for the UHR group were at least one attenuated psychotic symptom or at least one brief limited intermittent psychotic symptom assessed with Structured Interview for Prodromal Syndromes (SIPS; McGlashan, et al., 2001) . Further UHR inclusion criteria were >30% reduction in Global Assessment of Functioning (GAF; Endicott, Spitzer, Fleiss, & Cohen, 1976) and either schizotypal personality disorder or a first degree relative with psychosis. In the BIP group, participants had to score ≥14 points in the Hypomania Checklist (HCL; Angst, et al., 2005) or ≥12 points on the Hamilton Depression Rating Scale (HAMD; J. W. Williams, 1988) , or had a first degree relative with a history of bipolar disorder as well as a reduction of more than 30% in GAF during the past year. Furthermore, in addition to the clinical scales mentioned, the Positive Negative Symptoms Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and Beck Anxiety Inventory (Steer & Beck, 1997) were used. The HC was composed of individuals without history of any mental disorder, which was assessed with a face-to-face MINI Interview (Sheehan et al., 1998). The IQ was measured with multiple choice vocabulary test MWT-B (Lehrl, Triebig, & Fischer, 1995).

The participants were not included in the study if they presented with a bipolar disorder, manifest schizophrenia or organic or substance-induced psychosis. Moreover, substance or alcohol abuse, or IQ <80 were further exclusion criteria. From the initial fNIRS sample of 169 individuals, 18 were excluded due to insufficient quality caused by bad scalp contacts of the optodes and severe muscle artifacts. Furthermore, 6 participants were excluded from the behavioral analysis because of an error rate exceeding 33%. The detailed characteristics of the groups are presented in Table 1.

All participants gave written informed consent after being presented with the complete description of the study. For underage participants, parent's or guardian's informed consent was obtained additionally. The study was approved by the ethics committee of the Canton of Zurich and was conducted in accordance with the declaration of Helsinki.

Table 1. Demographic characteristic and emotional Stroop performance of the study groups

	HC	BIP	HR	UHR	*P*
n	46	16	41	48	
Gender (F:M)	22:24	4:12	14:27	19:29	> .05
Pre-morbid verbal IQ	107.7±12.5	105.8±10.2	102.4±11.4	100.1±13.3	< .01
Age	21.2±5.3	23.3±5.9	23.6±5.6	18.3±3.5	< .05
Reaction times (ms)					
Positive words	542.0 ± 88	742.7 ± 104	758.7 ± 95	780.2 ± 140	>.05
Negative words	538.1 ± 95	748.3 ± 88	767.2 ± 94	759.7 ± 140	ns
Neutral words	555.3 ± 92	738.1 ± 94	769.8 ± 87	777.0 ± 120	>.05
Error rate					
Positive words	2.5 ± 2.1	2.6 ± 2.3	2.9 ± 3.0	6.0 ± 6.0	>.05
Negative words	2.7 ± 2.1	3.3 ± 3.3	2.9 ± 3.1	5.6 ± 6.3	ns
Neutral words	2.8 ± 2.1	3.4 ± 2.6	3.1 ± 3.6	5.38 ± 5.6	ns

HC, healthy controls; BIP, high risk for bipolar disorder; HR, high risk for schizophrenia; UHR, ultra high risk for schizophrenia; F, female; M, male; ns, not significant.

Values given as mean ± standard deviation or number, and Bonferroni corrected p-values of $\chi 2$-test (gender), one-way measures analysis of variance (IQ, age, reaction times) and Kurskal-Wallis test (error rates) testing for group differences.

Emotional Stroop Task

The emotional Stroop task consisted of a total of 10 neutral (e.g. month, pencil), 10 positively (e.g. beauty, spring) and 10 negatively valenced (e.g. nightmare, death) words unrelated to any specific psychopathology. Each word was presented in red, green, blue and yellow on a black computer screen using Presentation software (Neurobehavioral Systems, Albany, CA). The words in all categories did not differ regarding the number of letters and syllables and their frequency in German language was similar. The words were presented randomly in an event-related design with the inter stimulus intervals varying between 4 and 8 seconds. Presentation of each word took 1500ms and was preceded by a white fixation cross shown for 500ms (Fig. 5). After the stimulus presentation the participants had to name the color of the word as fast as possible by pressing a corresponding color key on a keyboard. Before the actual task, the participants practiced the color-button correspondence by naming colors of 20 meaningless strings of letter X.

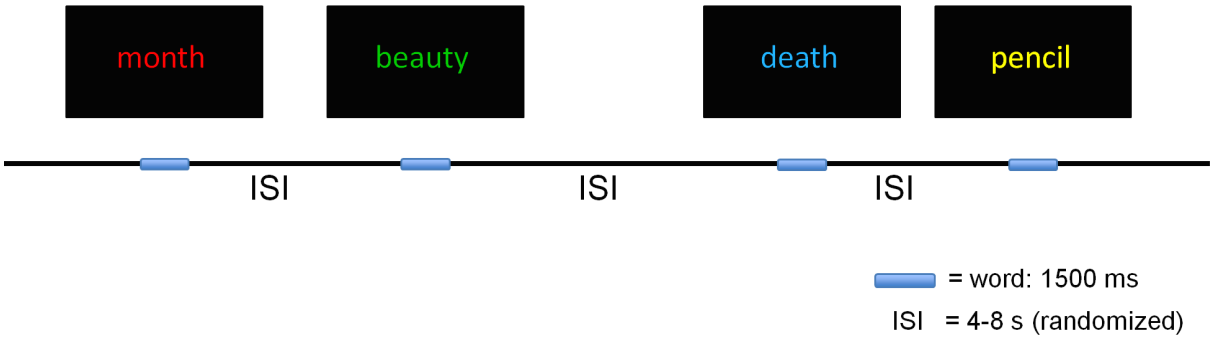

Figure 5. Schema of the emotional Stroop paradigm.

fNIRS

Changes in oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) were measured using the 52-channel ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan). A 3x11 channel probe set was placed on the participants' foreheads (see Fig. 6), so that the middle probe in the lowest row was placed a the Fpz position according to the international 10-20 System for electrode placement (Jasper, 1958). The near-infrared light was emitted in two wavelengths (695 ± 20nm and 830 ± 30nm) by 17 laser diodes and the relative changes of the reflected light were measured by 16 photo detectors. The sampling frequency of the recording was set to 10Hz. A modified Beer-Lambert Law (Delpy et al., 1988) was applied to transform the measured signal into the relative O_2Hb and HHb changes. A correlational based signal improvement (CBSI; Cui, Bray, & Reiss, 2010) and a band pass filter between 0.015 and 0.25 Hz were applied. Subsequently, channels containing artifacts or showing a flat line were interpolated. Moreover, after a visual inspection, segments with low signal to noise ratio were removed from further analysis. Estimated beta weights for O_2Hb were determined using the ordinary least squares regression analysis. The peak of the hemodynamic response was set to 6.5s after the stimulus onset.

Based on the previous fNIRS literature about the emotional Stroop (Tupak et al., 2013) we defined regions of interests (ROIs) located in the bilateral dorsolateral and medial prefrontal cortex (DLPFC, MPFC). Channels 8, 18, 19, 29 and 3, 13, 14, 24 were pooled in order to compute the parameters for the left and right DLPFC respectively. For the MPFC parameter channels 16, 26, 27, 37 were pooled. Furthermore, activation in bilateral frontotemporal cortices (FTC; pooled channels 32, 33, 34, 35, 43, 44, 45 and 39, 40, 41, 42, 50, 51, 52) was investigated, as these regions are involved in reading (Turkeltaub et al., 2002). The current

analysis focused on O_2Hb, as it is more sensitive to changes in the blood flow compared to HHb and it has been shown to deliver more stable results.

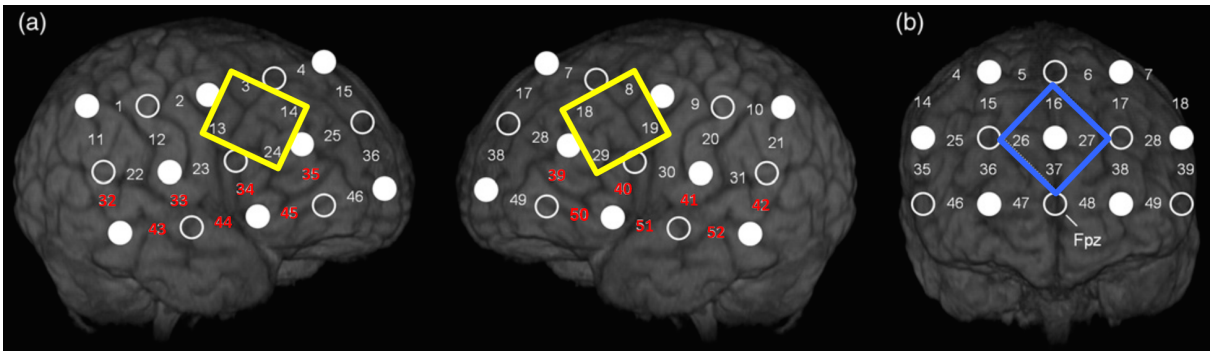

Figure 6. Positioning of the fNIRS probe set with measurement channels (numbers), light emitters (full circles) and light detectors (empty circles). Channels included in the regions of interests (ROIs): (a) bilateral dorsolateral prefrontal cortex (DLPFC, white frames), bilateral frontotemporal cortex (FTC; underlined channel numbers) and (b) medial prefrontal cortex (MPFC; gray frame). The position Fpz refers to the international 10-20 system of electrodes placement (Jasper, 1958). Adapted from Tupak et al. (2013)

Statistical analysis

A valence (positive, negative, neutral) × group (HR, UHR, BIP, HC) repeated measures ANOVA and Kurskal-Wallis test were applied to investigate the reaction times (RTs) and error rate (ER) respectively. The fNIRS O_2Hb data were each entered into a separate valence × group repeated measures analysis of variance (ANOVA). Subsequently, to compare differences between the groups for each condition and ROI separately, planned contrasts comparing the at risk groups against HC were conducted. Bonferroni correction was applied to correct for multiple comparisons. Furthermore, Pearason's correlations between the O_2Hb and behavioral data for all the regions of interests were computed. The significance level was set to $p < 0.05$ and trend-results were reported for $p < 0.1$.

The statistical analysis was performed using Matlab 2012b (The Math Works, Natick, MA) and SPSS 22.0 (IBM, SPSS Statistics, Munich, Germany).

5.1.4 Results

Task performance

The descriptive statistics of the performance data are depicted in the Table 1. The 3 × 4 repeated measures ANOVA revealed a significant main effect of the group for the RTs

($F(3,141) = 4.97$, $p < 0.005$). Planned contrasts revealed significantly slower RTs in UHR group compared to HC ($p < 0.001$) for all valences. Furthermore, planned contrasts showed a trend difference in the RTs between the HR and HC ($p < 0.1$). The ER showed a group difference only for positively valenced words ($H(3) = 11.25$, $p < 0.05$). Planned contrast revealed a significant difference between HC and UHR groups ($p < 0.05$).

O_2Hb changes in DLPFC & MPFC

The valence (positive, negative, neutral) × group (HC, HR, UHR, BIP) repeated measures ANOVA revealed a significant main effect of the group ($F(3,147) = 2.792$, $p < 0.05$) in the right DLPFC. Furthermore, trend main effect of the group was observed in the left DLPFC and MPFC ($F(3, 147) = 2.438$, $p < 0.1$ and $F(3, 147) = 2.256$, $p < 0.1$, respectively). However, no significant group × valence interactions were found.

The planned contrasts showed significantly lower O_2Hb measures in HR and UHR groups compared to HC in the right DLPFC, indicating lower brain activity ($p < 0.05$ for both HC-HR and HC-UHR comparisons). Moreover, significantly lower O_2Hb measures between all the at-risk groups and HC were found in the left DLPFC ($p < 0.05$ for HC-HR, HC-UHR and HC-BIP comparisons). In the MPFC planned contrasts revealed significantly lower O_2Hb measures for UHR compared to HC ($p < 0.05$).

A further post-hoc analysis revealed the group differences in the right DLPFC only for the negative words at a trend level for the HC-HR comparison ($p < 0.1$) and at the significant level for the HC-UHR comparison (Fig. 7).

Significant negative correlations ($r < -0.200$, $p < 0.05$) between O_2Hb measures and RTs were found in left and right DLPFC but only for neutral and positively valenced words. Furthermore, no significant correlations between O_2Hb measures and ER were observed.

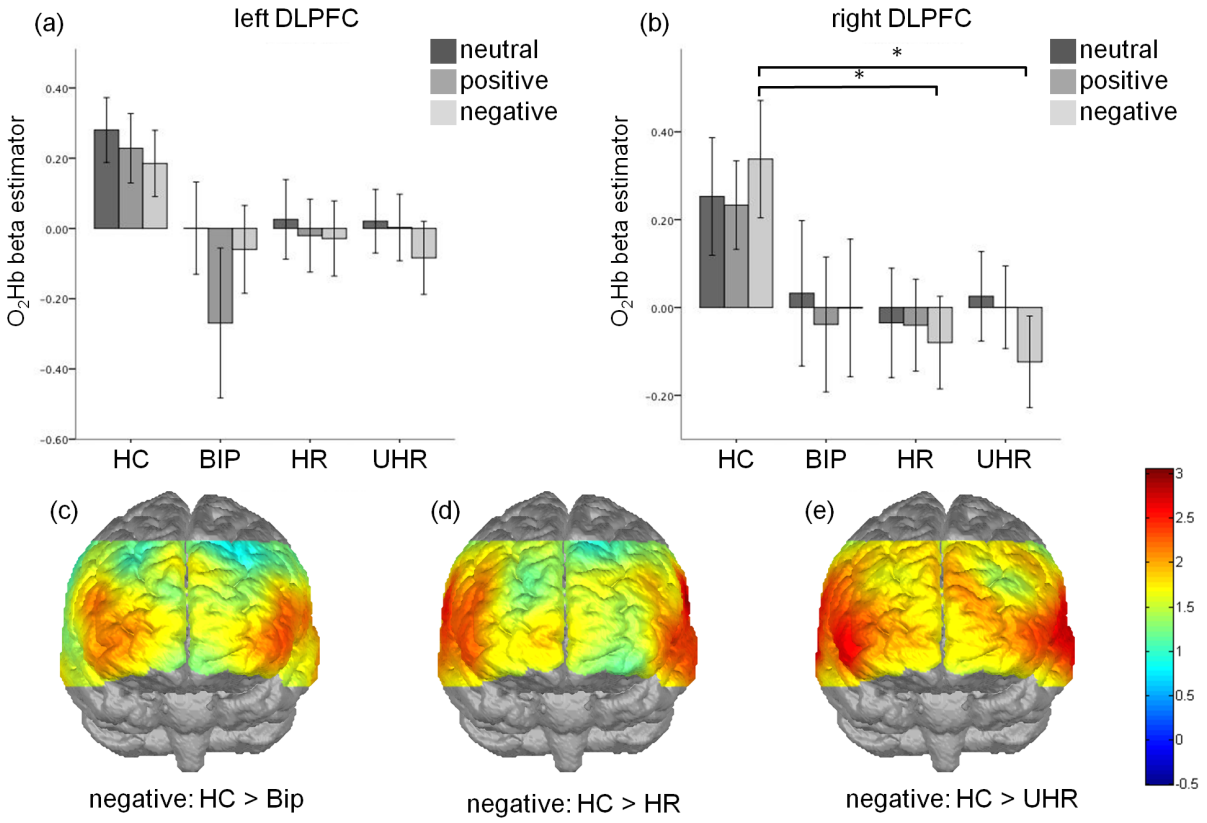

Figure 7. Effects of the group and valence on the dorsolateral prefrontal cortex (DLPFC) activation measured by the oxygenated hemoglobin levels (O_2Hb) in the left (a) and right (b) hemisphere. T-maps comparing the prefrontal activation elicited by the negative words for the HC and BIP (c), HR (d) and UHR (e) groups. * $p<0.05$.

O_2Hb changes in FTC

Significant main group effects were observed in left and right FTC ($F(3,147) = 6.058$, $p = 0.001$ and $F(3,147) = 6.775$, $p < 0.001$, respectively). Post-hoc tests revealed bilateral, significantly lower O_2Hb differences in all of the at-risk groups compared to the healthy controls. This finding was observed in all experimental conditions (Fig. 8). Furthermore, no differences between the at-risk groups were observed.

Pearson's correlations between the O_2Hb measures and RTs revealed significant associations ($r < -0.200$, $p < 0.05$) in the left and right FTC for all types of the words. ER revealed inconsistent results as, O_2Hb measures correlated only with positively valenced words in left and right FTC and with negatively valenced words in left FTC.

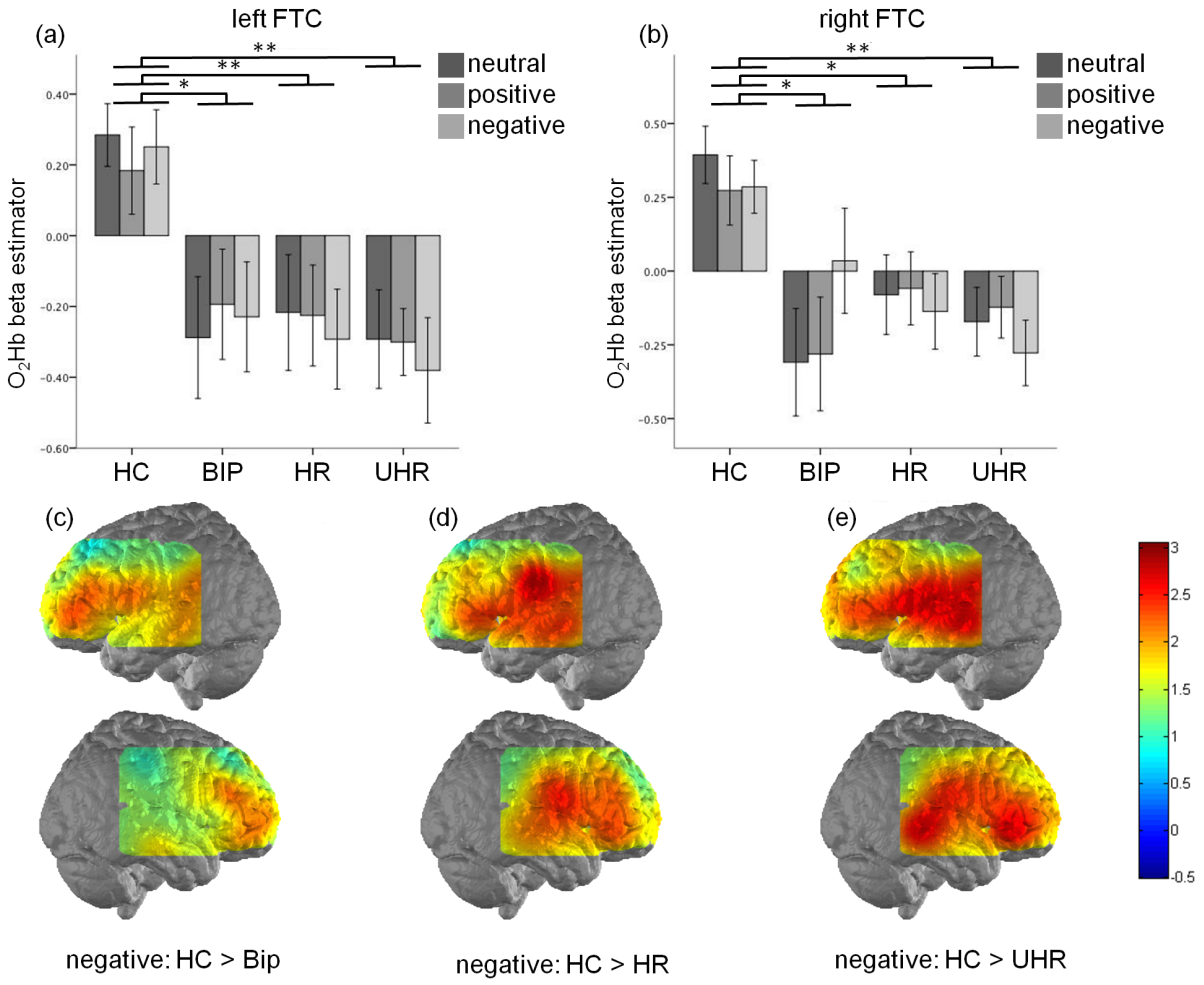

Figure 8. Effects of the group and valence on the frontotemporal cortex (FTC) activation measured by the oxygenated hemoglobin levels (O_2Hb) in the left (a) and right (b) hemisphere. Activation map showing higher levels of O_2Hb elicited by the negative words in the left and right hemisphere for the healthy controls compared to BIP (a), HR (b), UHR (c) groups. * $p<0.05$; ** $p<0.005$.

5.1.5 Discussion

The goal of the study presented here was to investigate the impact of emotionally valenced and neutral words on the frontal brain activity in individuals at-risk for schizophrenia and bipolar disorder. Presented results support the initial hypothesis of lower DLPFC activity, measured by changes in O_2Hb, in HR and UHR than in the HC group. Furthermore, lower activation in the bilateral FTC was observed in all of the at-risk groups compared to HC. These results are in line with our initial hypothesis, expecting lower FTC activation in the individuals at risk for schizophrenia.

Deficits in attentional processing in the individuals at risk for schizophrenia were observed already on a behavioral level. It is especially visible in the strong correlations between RTs and the FTC activity as well as the DLPFC activity. These findings could indicate that the deficits observed in the at-risk individuals are not only of behavioral but also of neurological nature.

The hypofrontality concept developed by Ingvar and Franzen (1974) describes a reduction of the functionality of the frontal brain in schizophrenia patients. This dysfunctionality has been widely demonstrated using various imaging techniques and during various neuropsychological tasks (e.g. Fallgatter and Müller, 2001; Perlstein, Dixit, Carter, Noll, & Cohen, 2003). Furthermore, hypofrontality has also been observed in first episode schizophrenia patients (e.g. Molina, et al., 2005; Pascual-Marqui, et al., 1999; Schneider, et al., 2007) . The results presented here are in line with these findings, as we observed lower DLPFC activity in the HR and UHR groups and lower MPFC activity in UHR group compared to HC. BIP group showed only slightly decreased activity in the left DLPFC compared to HC. These findings reflect a deficit in the prefrontal cortex during the emotional Stroop task, which could be related to specific deficits in performance. This assumption is supported by negative correlations between brain activation and RTs. However, it is unclear why these correlations are only present for positively and neutrally valenced words. Moreover, the results could indicate a general attention deficit, since the PFC is associated with attentional processes (Dresler et al., 2012). Therefore, it is possible that the HR and UHR groups were unable not to read the words actively on the screen (Dresler et al., 2012).

An interesting finding, which requires a further discussion, is the difference in O_2Hb beta estimators elicited by negatively valenced words between the two groups at risk for schizophrenia and the HC. Anxiety is a frequent symptom of the prodromal phase of schizophrenia, occurring often as a response to psychotic and other early symptoms (Yung & McGorry, 1996a, 1996b). Therefore, we expected to obtain similar results as those reported for anxiety prone individuals or anxiety patients. In an fNIRS study with anxiety prone individuals Tupak et al. (2013) assumed that lower DLPFC activity reflects an inability to inhibit the amygdala response to fear-related stimuli. A similar explanation could also be applied to our findings showing a decreased right DLPFC activity in HR and UHR groups compared to HC, as a response to negative words. However, since fNIRS can only measure cortical activity, this interpretation remains theoretical. Only a few studies have used fMRI

during the emotional Stroop task and even those report some contradictory results. Dresler et al. (2012) did not find any differences in the amygdala activity between panic patients and healthy controls, whereas Malhi, Lagopoulos, Sachdev, Ivanovski, and Shnier (2005) showed a decreased activation in left temporal cortex and amygdala in the euthymic bipolar disorder patients. Furthermore, a review study by Jaworska, Yang, Knott, and MacQueen (2014) reported an increased amygdala activity as a response to negative stimuli in depressed patients.

Frontal and temporal activation during the emotional Stroop task has been reported in various studies with healthy individuals and anxiety patients (Compton et al., 2003; Dresler et al., 2012). The temporal cortex has been associated with semantic processing (Whitney, Kirk, O'Sullivan, Ralph, & Jefferies, 2011) as well as reading and language (Fallgatter & Strik, 1998; Perani et al., 1999; S. Schneider et al., 2015; Tyler, Russell, Fadili, & Moss, 2001). Since lower FTC activity was found in all the at-risk individuals, it would suggest that all of them have reading or language related deficits, beyond the verbal IQ assessed in this study. This explanation is supported by negative correlations between FTC activation and the performance measures (RTs and ER). RTs correlations seem to be stable across different types of words, which further indicates a valence-independent processing deficit. Nevertheless, it is somewhat surprising that no differences between the individuals at-risk for schizophrenia and bipolar disorder were found.

Nonetheless, all the findings have to be interpreted with caution as this study poses several limitations. First, the definition of the at-risk stage for bipolar disorder is not well researched and no consistent description has been developed (D. J. Martin & Smith, 2013). The definition used in the present study is based on a continuum from depression to mania, focusing on the whole spectrum of the disorder (Angst et al., 2005). Second, UHR individuals differed from the other groups regarding their age and IQ. It is regarded as a limitation, since the task involved frontal cortex, which is still developing at the young age. Furthermore, since the task required written words it is possible that the IQ differences could influence the results. However, because of the significant group differences an analysis of covariance (ANCOVA) is not the appropriate solution, as it is explained by G. A. Miller and Chapman (2001). An explanation for the lower age and IQ in the UHR group can be that individuals with the highest risk for schizophrenia have more severe underlying deficits causing them to exhibit the symptoms earlier compared to other individuals. Nevertheless, most of the

statistically significant results showed that both at-risk for schizophrenia groups differ from HC group, which indicates that the results are related to the underlying pathology rather than the age, as only the UHR individuals were significantly younger than HC. Furthermore, a minor limitation is connected to the fNIRS, as it only allows investigating cortical processes and not the subcortical structures involved in emotional processing.

Future research will include a follow-up study investigating various ways of progression of the individuals' at-risk status in relation to the emotional processing and brain activity. This could not only advance our understanding of the functioning of the PFC and FTC but also help establishing a diagnostic tool for the identification of individuals in the prodromal phase of a psychosis. Moreover, it would be interesting to examine, if processing of emotional words related to the symptoms of particular disorder could be more distinctive for a disorder than when just positive and negative words are used.

5.1.6 Conclusions

To our knowledge this is the first study investigating frontal brain activation elicited by the emotional Stroop task using fNIRS in individuals at risk for schizophrenia and bipolar disorder. The HR and UHR groups differed from the HC regarding lower bilateral DLPFC and FTC activity as well as longer RTs, whereas individuals in the BIP group only differed with the respect to left DLPFC and FTC activity. These findings show that the neurophysiological differences regarding emotional processing appear as early as the at-risk state for mental disorders. Moreover, prolonged RTs to all three types of words, found in HR and UHR groups, indicate emotional processing deficits only in the individuals at risk for schizophrenia. Nevertheless, follow-up research investigating the transition from the at-risk phase to manifest psychosis is needed to further analyze the neurophysiological and neuropsychological changes.

5.2 Study II: Verbal Fluency Test

Title

Different frontal brain activation during verbal fluency test in individuals at risk for schizophrenia and bipolar disorder: A functional near-infrared spectroscopy study

Authors

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5.2.1 Abstract

Background

The verbal fluency task (VFT) is a well-established type of word production test requiring activation of the prefrontal cortex (PFC) in healthy persons. Previous studies have reported worse VFT performance and lower PFC activation in patients with manifest schizophrenia than in healthy individuals. Our goal was to investigate performance and PFC activation during phonemic and semantic VFT in individuals at risk for schizophrenia and bipolar disorder. Furthermore, we compared these results with healthy individuals.

Methods

Three at-risk groups were included in the analysis: at-ultra-high risk for schizophrenia (UHR; n=44), at-risk for schizophrenia (HR; n=40), at-risk for bipolar disorder (BIP; n=16), along with a healthy control group (HC; n=35). Functional near-infrared spectroscopy was applied to measure brain activation. The subsequent analysis focused on the activation in the bilateral PFC.

Results

All individuals at risk for schizophrenia produced fewer words than healthy controls. In addition, the UHR group showed lower PFC activation at the trend level than the HC group. Furthermore, both groups at risk for schizophrenia showed lower PFC activation than the BIP group.

Conclusions

The results indicate that functional PFC deficits known in schizophrenia appear as early as the at-risk stage for psychosis. Moreover, lower PFC activation in the HR and UHR groups than in the BIP group suggest different neurophysiological mechanisms underlying the disorders.

5.2.2 Introduction

Neuropsychological deficits are common symptoms in individuals suffering from schizophrenia and bipolar disorder (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Nuechterlein, Ventura, Subotnik, & Bartzokis, 2014). They not only impact social outcomes, but can also influence potential treatment responses (Green, Kern, Braff, & Mintz, 2000). Furthermore, neuroimaging studies have shown alterations in brain functioning that mirror the cognitive deficits (Antonova et al., 2005; Eich, Nee, Insel, Malapani, & Smith, 2014; Fallgatter & Strik, 2000). These alterations are especially prominent in the prefrontal cortex (PFC). In schizophrenia patients, an underactivation of the PFC, termed hypofrontality (Ingvar & Franzen, 1974), has often been described in neuroimaging studies (Curtis et al., 1998; Ehlis et al., 2007; Fallgatter & Müller, 2001). Hypofrontality has also been reported in individuals at risk for schizophrenia (e.g., Walton et al., 2013). However, hyperactivation of the PFC has also been described (e.g., Tanaka 2008). Therefore, it poses an interesting marker for early recognition of this disorder.

The verbal fluency task (VFT) is a neuropsychological test known to involve various cognitive processes and PFC activation (Troyer et al., 1997; Tupak et al., 2012), which makes it a well-suited and interesting task for schizophrenia research. There are two versions of VFT – semantic and phonemic VFT. These require different cognitive skills to retrieve appropriate words (Troyer et al., 1997). Furthermore, it has been shown that, even though the PFC is activated during VFT, the distribution of activation in the cortex might vary between the phonemic and semantic versions (Kubota et al., 2005; Tupak et al., 2012). In healthy individuals, Tupak et al. (2012) reported increased activation in bilateral frontotemporal cortex (FTC) for semantic and phonemic VFT, whereas increased activation in anterior and superior PFC was observed only during the phonemic VFT. Contradictory, Kubota et al. (2005) showed greater PFC activation for the semantic than the phonemic VFT in healthy individuals. Furthermore, in this study, schizophrenia patients showed an opposite pattern (Kubota et al., 2005). However, these results have not yet been replicated (Ehlis et al., 2007).

Previous studies investigating schizophrenia patients reported that the patients produced generally fewer words during the VFT than healthy controls (Henry & Crawford, 2005). Furthermore, schizophrenia patients showed lower PFC activation than healthy controls during phonemic and semantic VFT (Ehlis et al., 2007; Kubota et al., 2005). Few studies have investigated PFC activation during VFT in patients suffering from bipolar disorder.

Moreover, bipolar disorder is usually grouped together with major depressive disorder. Nevertheless, decreased PFC activation during VFT has been described in this group of patients too, as it is pointed out by Dieler et al. in a general review article (Dieler et al., 2012).

Functional near-infrared spectroscopy (fNIRS) is a neuroimaging method suitable for investigating brain activation in tasks requiring active speech, such as the VFT. It is a relatively new imaging method, which is rapidly gaining popularity in neuropsychological and psychiatric research (Ehlis et al., 2014). It uses near-infrared light to measure relative changes in concentration of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb), which, similar to the BOLD signal, can be used as estimates of brain activation (Obrig & Villringer, 2003). Despite low spatial resolution (Cui, Bray, Bryant, Glover, & Reiss, 2011), fNIRS is relatively insensitive to movement, allowing a simultaneous recording of behavioral performance and brain activation. This is undoubtedly the main advantage of fNIRS, as other imaging methods (e.g., functional magnetic resonance imaging, fMRI) are more sensitive to movement and not well suited for tasks involving motor responses. Therefore, in our study we were able to conduct a spoken VFT, which was more difficult in fMRI studies, during which the covert VFT is preferred (Curtis et al., 1998; Weiss et al., 2004; Weiss et al., 2003).

Despite some evidence of cognitive and neurological deficits observed during the at-risk stage of schizophrenia and bipolar disorder (Dazzan et al., 2012; Metzler et al., 2014; Roberts et al., 2013; Sprooten et al., 2011; Whalley et al., 2004), previous studies investigating brain activation during VFT have mostly focused on patients with manifest disorders. The goal of this study was to investigate frontal brain activation during semantic and phonemic VFT in individuals at risk for schizophrenia and bipolar disorder. Based on previous findings, we expected to observe decreased performance in all at-risk groups compared to healthy controls. Moreover, we expected the deficits to be especially prominent for the phonemic VFT as it requires more complex word-retrieval mechanisms (Ehlis et al., 2007). On the neurophysiological level, we expected to observe a reduced increase in O_2Hb concentration during task performance, indicating lower PFC activation, in all at-risk groups. Since the literature comparing performance and neurophysiology during VFT in schizophrenia and bipolar disorder patients is scarce, we did not hypothesize about differences in brain activation between these at-risk groups.

5.2.3 Methods and Materials

Participants

This study is a part of prospective, longitudinal early recognition study within the Zurich Program for Sustainable Development of Mental Health Services (ZInEP) concerning the early detection of at-risk states for psychotic and bipolar disorders. Participants between the age 13 and 35 were recruited at four early recognition centers in the Canton of Zurich. The age, sex, and IQ-matched healthy controls (HC) were recruited from the general population. The methodological details of the ZInEP early recognition study are described by Theodoridou et al. (2014).

The at-risk participants of the study were divided into the three groups: at high risk for schizophrenia (HR), at ultra-high risk for schizophrenia (UHR) and at risk for bipolar disorder (BIP). The participants were included in these groups if at least one of the criteria mentioned below was fulfilled.

The HR inclusion was assessed using the adult or children-youth versions of the Schizophrenia Proneness Interview (SPI-A, SPI-CY, Schultze-Lutter et al., 2007; Schultze-Lutter & Koch, 2010). The individuals were included in the HR group if they experienced at least one cognitive-perceptive (COPER) basic symptom or at least two cognitive disturbance symptoms (COGDIS).

For the UHR assignment, a Structured Interview for Prodromal Syndromes (SIPS, McGlashan et al., 2001) was applied, and individuals with at least one attenuated psychotic symptom or at least one brief limited intermittent psychotic symptom were included in this group. Further inclusion criteria were at least 30% reduction in Global Assessment of Functioning (GAF, Endicott et al., 1976) and either schizotypal personality disorder or a first-degree relative with psychosis.

The BIP inclusion criteria were fulfilled when individuals scored ≥ 14 points in the Hypomania Checklist (HCL, Angst et al., 2005) or ≥12 points on the Hamilton Depression Rating Scale (HAMD, J. W. Williams, 1988) , or had a first-degree relative with a history of bipolar disorder as well as a reduction of more than 30% in GAF during the past year.

Participants were excluded from the study if they presented with a diagnosis of manifest schizophrenia, bipolar disorder, organic or substance-induced psychosis or alcohol abuse. Moreover, individuals were excluded if their IQ was below 80 assessed with multiple choice vocabulary test MWT-B (Lehrl et al., 1995). In addition to these exclusion criteria, participants were excluded from the HC group if they presented with a history of a mental disorder as assessed with a face-to-face MINI Interview (Sheehan et al., 1998) or had a family member with a positive history of mental disorders.

From the initial fNIRS sample of 167 individuals, 32 were excluded due to insufficient data quality caused by an insufficient contact between the optodes and/or the scalp and severe muscle artifacts. The detailed characteristics of the groups are presented in Table 2. The UHR group differed significantly from the other groups regarding age and IQ. It was most likely caused by sampling protocols, as the individuals in the at-risk groups were first included in the study and subsequently assigned to the groups.

All participants gave written informed consent after being presented with the complete description of the study. In case of minors, parent's or guardian's informed consent was obtained. The study was approved by the Ethics Committee of the Canton of Zurich and was conducted in accordance with the Declaration of Helsinki.

Table 2. Demographic characteristic

	HC	BIP	HR	UHR	*p*-value
n	35	16	40	44	
Gender (F:M)	13:22	4:12	14:26	18:26	ns
Verbal IQ	108.5 ± 13.3	110.1 ± 12.1	104.2 ± 12.1	100.2 ± 13.0	$p < .05$
Age	21.9 ± 5.7	22.9 ± 6.7	23.7 ± 5.9	18.4 ± 3.91	$p < .001$

HC, healthy controls; BIP, high risk for bipolar disorder; HR, high risk for schizophrenia; UHR, ultra high risk for schizophrenia; F, female; M, male; ns, not significant

Values given as mean ± standard deviation or number.

Verbal fluency test

Phonemic and semantic verbal fluency test (VFT), and a control task were used in a counterbalanced block design. The whole measurement consisted of three 30s-long trials per condition, which were separated by 30s-long breaks, yielding nine experimental blocks and

nine breaks. The first block was preceded by a 10s baseline measurement. During the VFT, the participants were asked to name German nouns beginning with the letter A, F or S respectively (phonemic VFT) or belonging to one of the respective semantic categories: animals, fruits or flowers (semantic VFT). During the control task, the participants were asked to name days of the week in the correct sequence. The pace of the control task was indicated by the experimenter to approximately match the number of words produced during the VFT. The VFT design followed the one described by (Herrmann, Ehlis, & Fallgatter, 2003).

fNIRS

Changes in oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) were measured using the 52-channel ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan). The 3×11 probe consisted of 17 semi-conductive laser diodes, emitting near-infrared light in two wavelengths (695 ± 20 nm and 830 ± 30 nm), and 16 photo detectors, which measured changes in the reflected light. The probe covered the prefrontal and temporal cortex (Fig. 9) and was positioned so that the middle optode of the lowest row was placed at the Fpz position according to the international 10-20 System for electrode placement (Jasper, 1958). The sampling frequency of the recording was set to 10 Hz.

A modified Beer-Lambert Law (Delpy et al., 1988) was applied to transform the measured signal into the relative O_2Hb and HHb changes. A band pass filter was set between 0.008 and 0.05 Hz. Subsequently, channels containing artifacts or showing a flat line were interpolated. Additionally, during a visual inspection of the data, task-blocks showing a low signal to noise ratio were removed from further analysis.

For each condition, the blocks were averaged and subsequently further signal time course averages for each condition, participant, and channel were computed. The segments started 3s after the beginning of each task and lasted until the end of a block. These values were baseline corrected by subtracting the averaged activation during the first 0.5s of the each task. The bilateral prefrontal cortices (PFC) were defined as the regions of interest (ROIs) based on the previous literature (Tupak et al., 2012). Channels 4, 5, 14, 15, 25, 26, 36 and 6, 7, 17, 18, 27, 28, 38 were pooled in order to compute the parameters for the left and right PFC respectively (Fig. 9). The analysis of the brain activation focused only on O_2Hb data, as it is said to deliver more consistent results then HHb (Dieler et al., 2012).

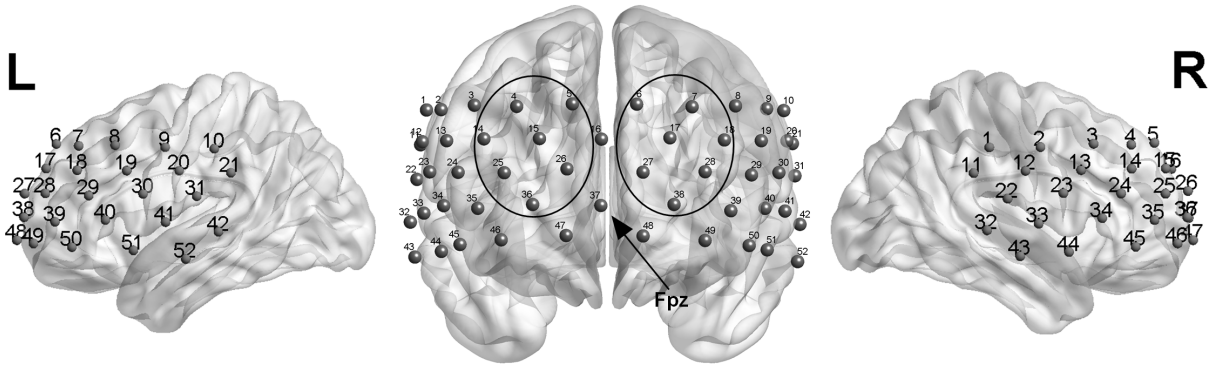

Figure 9. Positioning of the fNIRS probe with positions of the channels (grey circles and numbers) used in the study. Channels included in the regions of interest (prefrontal cortex) are circled (channels 4, 5, 14, 15, 25, 26, 36 and 6, 7, 17, 18, 27, 28, 38 for the left and right prefrontal cortex respectively). The position Fpz is localized according to the international 10-20 system of electrodes placement (Jasper, 1958).

Statistical analysis

The statistical analysis was performed using Matlab 2012b (The Math Works, Natick, MA) and SPSS 21.0 (IBM, SPSS Statistics, Munich, Germany).

Repeated-measures analysis of variance (ANOVA) was used to investigate the group differences in produced words and brain activation. If the sphericity assumption was not met, the degrees of freedom were corrected using the Greenhousse-Geisser method. Since number of repetitions and rule breaks were not normally distributed, nonparametric equivalent of ANOVA (Kruskal-Wallis test) was used. In case of significant main effects, post-hoc tests were Bonferroni corrected to account for multiple testing. Pearson's correlation was applied to investigate the relationship between the performance and brain activation. The significance level was set for $p < .05$ and the trend level for $p < 0.1$.

5.2.4 Results

Task performance

The descriptive statistics of the performance data are depicted in Table 3. In the statistical analysis the factor task consisted of the performance during the phonemic and semantic VFT, and factor group of the BIP, HR, UHR and HC groups. The task × group repeated-measures ANOVA showed a significant main effect of group ($F_{3,131} = 9.04$, $p < .001$) and task ($F_{1,131} =$

1012.18, $p < .001$). Furthermore, a significant group × task interaction was found ($F_{3,131} = 14.06$, $p < .001$). Post hoc tests showed that HR and UHR individuals produced significantly fewer words than HC ($p < .05$ and $p < .001$ respectively), for both semantic and phonemic VFT (Fig. 10). Moreover, the BIP group performed significantly better than the UHR group ($p < .05$). To further examine the significant interaction effect, we compared word production during the semantic and phonemic VFT separately. The post-hoc tests showed that the BIP group produced more words than the UHR group only for the phonemic VFT ($p < .05$). No differences were found between the groups or tasks regarding the number of repetitions or rule breaks.

Table 3. Performance in phonemic and semantic verbal fluency task

	HC	BIP	HR	UHR	*p*-value
Phonemic VFT					
Produced words	6.6 ± 1.6	6.2 ± 2.2	5.4 ± 2.1	4.6 ± 1.8	<.001
Repetitions	0.3 ± 0.4	0.3 ± 0.3	0.1 ± 0.2	0.2 ± 0.2	ns
Rule breaks	0.6 ± 0.6	0.4 ± 0.5	0.6 ± 0.8	0.9 ± 1.2	ns
Semantic VFT					
Produced words	10.7 ± 2.1	10.3 ± 2.0	9.3 ± 2.1	8.7 ± 2.6	ns
Repetitions	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	ns
Rule breaks	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.6	0.3 ± 0.8	ns

Abbreviations: VFT, verbal fluency task; HC, healthy controls; BIP, high risk for bipolar disorder; HR, high risk for schizophrenia; UHR, ultra high risk for schizophrenia; ns, not significant

Values are given as means ± standard deviations

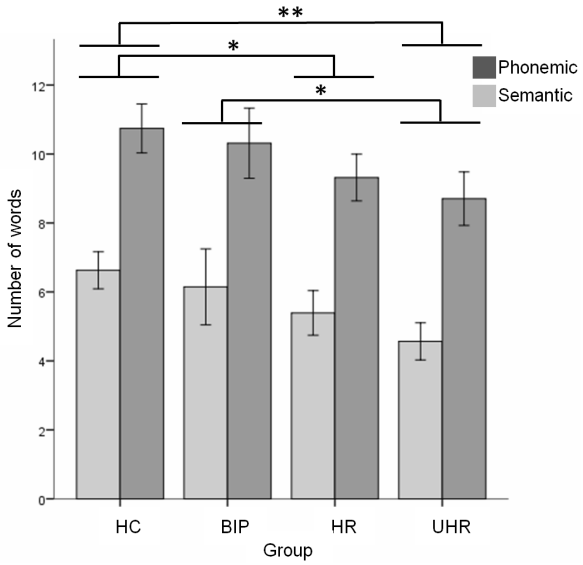

Figure 10. Words produced during the phonemic and semantic verbal fluency test (VFT) in the four study groups. Abbreviations: HC, healthy controls; BIP, high risk for bipolar disorder; HR, high risk for schizophrenia; UHR, ultra high risk for schizophrenia.
* $p < 0.05$, ** $p < 0.001$

O_2Hb changes in the PFC

In the statistical analysis, the factor task consisted of the brain activation during the phonemic VFT, semantic VFT and control task, and factor group of the BIP, HR, UHR and HC groups. The task × group repeated-measures ANOVA for the O_2Hb increase showed significant results only in the left PFC. A significant main effect of task and group, as well as a task × group interaction were found ($F_{1.9,248.4} = 16.96$, $p < .001$, $F_{3,131} = 3.65$, $p < .01$, $F_{5.69,\ 248.4} = 2.80$, $p < .01$, respectively). The post-hoc tests showed higher O_2Hb increases for both phonemic and semantic VFT than in the control task ($p < .001$ and $p < .001$ respectively). The post-hoc tests for the main effect of the group showed a significantly smaller O_2Hb increase in the UHR group than in the BIP group ($p < .05$) and smaller increase at the trend level in the UHR group than in the HC group ($p < .1$).

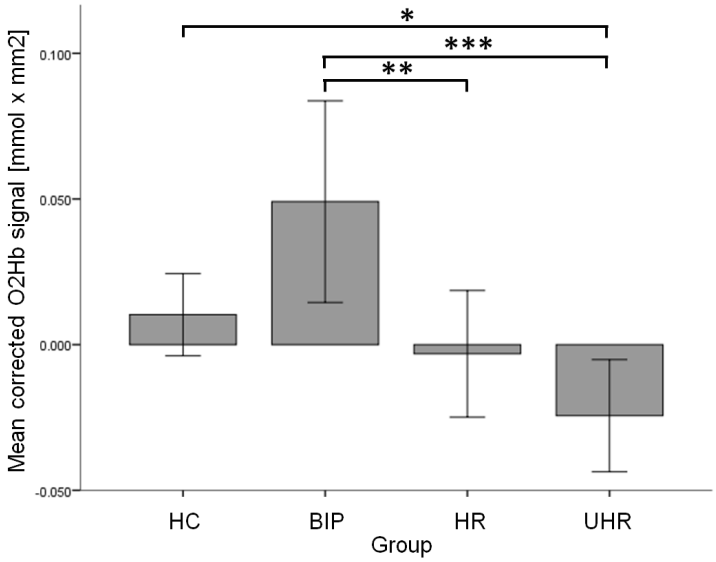

Figure 11. Increase in the levels of the oxygenated hemoglobin (O_2Hb) in the left prefrontal cortex (PFC) in the four study groups. Abbreviations: HC, healthy controls; BIP, high risk for bipolar disorder; HR, high risk for schizophrenia; UHR, ultra high risk for schizophrenia.
* p < 0.1, ** p < 0.05, *** p < 0.001

To better understand the significant interaction effect, one-way ANOVA was computed separately for each task. Significant differences between the groups were found only for the phonemic VFT ($F_{3,131}$ = 6.11, p >.001) and mirrored the differences observed for the main effect of the group (Fig. 11). The UHR group showed a smaller O_2Hb increase compared to the BIP group (p < .001) and a smaller O_2Hb increase at the trend level compared to the HC group (p < .1). Furthermore, significantly smaller O_2Hb increase in the HR group than in the BIP group was found (p < .05). Figure 12 shows the t-maps depicting the comparisons between the HC group and the at-risks groups for the phonemic VFT.

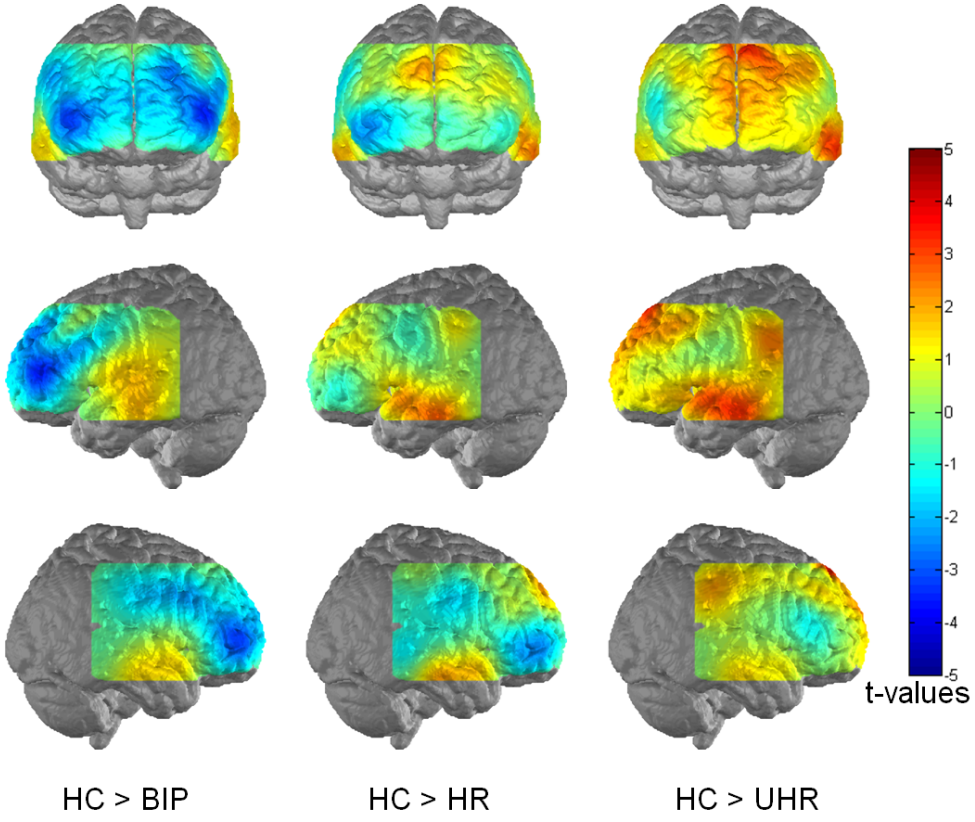

Figure 12. *t*-maps comparing the prefrontal activation elicited during the semantic verbal fluency test (VFT) for the healthy controls (HC) and (a) high risk for bipolar disorder (BIP), (b) high risk for schizophrenia (HR) and (c) ultra high risk for schizophrenia (UHR) group.

Pearson's correlations between O_2Hb increase and task performance were only significant during the phonemic VFT. Positive correlations were found between the performance and left and right PFCs ($r = .247$, $p < .01$ and $r = .179$, $p < .05$ respectively).

To investigate a potential effect of age on the results, age was integrated as a covariate into the task × group ANOVA model. The results showed no significant influence of age, which was additionally confirmed by not significant correlations between age and PFC activation.

5.2.5 Discussion

In the current study, we applied functional near-infrared spectroscopy (fNIRS) to simultaneously measure performance and prefrontal cortex (PFC) activation during phonemic

and semantic verbal fluency tasks (VFTs) in individuals at risk for schizophrenia and bipolar disorder. Both groups at risk for schizophrenia, high risk (HR) and ultra high risk (UHR), produced significantly fewer words during both types of VFT than the healthy control (HC) group. Furthermore, the performance during the phonemic VFT correlated positively with the activation in both PFCs. In line with our hypotheses, the UHR group showed decreased left PFC activation at the trend level compared to the HC group during the phonemic VFT. However, the PFC activation in the HR group did not differ from the HC group. Interestingly, the group at risk for bipolar disorder (BIP) showed higher left PFC activation than the HR and UHR groups during the phonemic VFT. These findings were partially mirrored by significantly better performance in the BIP group than the UHR group during the phonemic VFT. This could indicate not only behavioral differences but also underlying neurophysiological differences between individuals at risk for these two disorders, which requires further discussion.

The differences in the left PFC activation between the BIP group and the groups at risk for schizophrenia are perhaps the most intriguing findings of this study. So far, no fNIRS studies have directly compared PFC activation in bipolar and schizophrenia patients or at-risk individuals. However, in an fMRI study, (Curtis et al., 2001) described increased prefrontal activation in bipolar patients compared to healthy individuals and schizophrenia patients during the VFT. Their results are in line with our findings. Nevertheless, the fMRI study by Curtis et al. (1998); Curtis et al. (2001) only allowed for a covert VFT, and the actual performance was not investigated. In our study, the difference in PFC activation between the BIP and the UHR groups is mirrored by the VFT performance. This indicates that neurophysiological and cognitive differences between bipolar disorder and schizophrenia can be observed as early as the at-risk stage.

Not surprisingly, the left PFC was significantly more activated during both VFT tasks compared to the control task in all groups. This reflects involvement of complex word-retrieval mechanisms during the VFT and automatic word production during the control task (Ehlis et al., 2007). Furthermore, the UHR group showed decreased left PFC activation during all tasks compared to the HC group, which was in line with our initial hypothesis and the hypofrontality concept (Ingvar & Franzen, 1974). Most studies with manifest schizophrenia patients have described decreased PFC activation compared to healthy individuals for both types of VFT (Ikezawa et al., 2009; Takizawa et al., 2009; Takizawa et al., 2008). However,

more pronounced differences between patients and control subjects were observed during the phonemic VFT (Ehlis et al., 2007; Tupak et al., 2012). Therefore, it is not surprising that the difference in PFC activation between the UHR and HC groups was observed during the phonemic VFT rather than the semantic VFT. Furthermore, the findings would suggest that the UHR individuals searched directly for the appropriate words instead of word-retrieval applying strategies (e.g., focusing on semantic or phonemic properties) used by healthy individuals reflected in the activation of the prefrontal cortex (Ehlis et al., 2007). Even though the differences between the groups were observed only at the trend level, they suggest that neurophysiological dysfunctions can be observed in individuals at risk for schizophrenia, before the disorder becomes fully manifest.

Significant correlations between performance and increase of O_2Hb levels in bilateral PFC were observed only during the phonemic VFT. These results suggest a strong link between PFC activation, observed cognitive performance and potentially used word retrieval strategies. The phonemic word retrieval strategies contrast with category-guided retrieval of words during semantic VFT, which probably activates more temporal brain regions (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004). Previous studies have described similar associations between dysfunctions in the prefrontal cortex activation and word-retrieval during the VFT in healthy individuals and schizophrenia patients (Obayashi & Hara, 2013; Quaresima, Giosuè, Roncone, Casacchia, & Ferrari, 2009).

The performance results presented in this study are in line with the literature (Bokat & Goldberg, 2003; Henry & Crawford, 2005; Quraishi & Frangou, 2002). We found lower word production during the phonemic VFT compared to the semantic VFT in all the groups. A possible explanation of this phenomenon is that the phonemic VFT requires more effort to activate the word-retrieval strategies (A. Martin, Wiggs, Lalonde, & Mack, 1994). The deficits in VFT performance in both groups at risk for schizophrenia compared to the HC group were also in line with the literature and our initial hypothesis. This shows that the cognitive deficits observed in manifest schizophrenia patients (Bokat & Goldberg, 2003; Henry & Crawford, 2005) are also present in individuals at risk for the disorder. The performance of the BIP group did not differ from the healthy controls, but the group performed significantly better than the HR and UHR groups during the phonemic VFT. This could indicate underlying cognitive differences during the at-risk stage of schizophrenia and bipolar disorder.

Limitations and further research

Nonetheless, the findings presented here have to be interpreted with caution, as the study exhibits several limitations. The UHR group differed significantly from the other groups regarding age and IQ, which could have an influence on individuals' performance and PFC activation. However, the performance deficits were also observed in the HR group, as was the significantly lower PFC activation in the HR compared to the BIP group. Significantly lower age and IQ in the UHR group can be explained by the underlying psychopathology, which is more severe in this group and causes the deficits to manifest earlier and/or to search for medical help. Because of this assumption and significant differences between the groups the analysis of covariance, with age and IQ as covariates, is not the appropriate statistical analysis (for detailed explanation see G. A. Miller and Chapman (2001)). Therefore ANOVA without covariates was applied in this study. A further minor limitation is related to the unequal sizes of the groups, especially small BIP group. During the recruitment there were no restrictions regarding the groups' sizes and all individuals who came to the early recognition centers were included in the study.

Further research validating the results presented here is still needed. In a follow-up study, currently under analysis, we want to investigate the frontal brain activation in those individuals who subsequently progressed to manifest schizophrenia and bipolar disorder.

Conclusions

This study is one of the first to examine brain activation during the VFT in individuals at risk for schizophrenia and bipolar disorder. The most interesting finding is increased left PFC activation in the BIP group compared to both groups at risk for schizophrenia, which could indicate different PFC alterations in the at-risk stage for these two disorders. Furthermore, higher PFC activation in the BIP group than the UHR group was mirrored by significantly better performance in the BIP group. Even though the performance deficits in the HR and UHR groups compared to healthy controls were observed for both the phonemic and semantic VFT, the neurophysiological differences were observed only during the phonemic task and only between the UHR and HC groups. Current findings could indicate that the individuals at risk for schizophrenia and bipolar disorder show cognitive differences on behavioral and neurophysiological level, which in turn could contribute to a better discrimination between

these disorders in early stages. Furthermore, fNIRS is an uncomplicated and inexpensive method, which allows easy investigation of these cognitive differences.

6. General discussion

Early recognition of schizophrenia and bipolar disorder has been a hot research topic over the last few decades. Aiming at identifying and treating at-risk individuals, researchers have attempted to decrease the duration of untreated psychosis (DUP) and through that to improve individual's outcomes. This dissertation contributes to the previous early recognition research by investigating the prefrontal brain activation during two neuropsychological tasks in individuals at risk for schizophrenia and bipolar disorder in search for possible biomarkers or risk factors.

Employing functional near-infrared spectroscopy (fNIRS) allowed us to obtain simultaneous behavioral and imaging data during an overt language task in Study 2. Furthermore, this method was well fitted for the study population, which mostly consisted of teenagers and young adults, who may have had problems with restricted movement ability during a long and tiring experiment. Furthermore, participants' preparation time was short and did not add more burden to the experimental procedure.

Both studies presented in this dissertation focused especially on the prefrontal cortex (PFC) activation in individuals at high and ultra high risk for schizophrenia, at high risk for bipolar disorder, and in healthy individuals. Individuals at risk for schizophrenia were divided into two groups based on psychopathological symptoms. Individuals in the high risk group fulfilled the basic symptoms criteria assessed with the Schizophrenia Proneness Instrument (Schultze-Lutter, Addington, et al., 2007; Schultze-Lutter & Koch, 2010), whereas those in the ultra-high risk group exhibited attenuated positive symptoms and brief limited intermittent psychotic episodes described by Yung and McGorry (1996b) as assessed with the Structured Interview for Prodromal Symptoms (T. J. Miller et al., 2003).

Study 1 focused on processing of emotional words and emotional interference. The aim was to investigate the dorsolateral prefrontal and frontotemporal brain activation during emotional Stroop task. Study 2 investigated prefrontal activation and cognitive performance during semantic and phonemic verbal fluency task (VFT). The findings provided by both of these studies contribute to our understanding of the neurophysiological processes in the at-risk stage for schizophrenia and bipolar disorder. Furthermore, the findings can be used as a first step in the search for biomarkers that could contribute to the early recognition of these two disorders.

6.1. Emotional Stroop

Emotional Stroop is a modified version of the classic Stroop task, which has been thoroughly described in literature. On the behavioral level, emotional interference elicited by the task has been observed in various patient groups (J. M. G. Williams et al., 1996). The most prominent results have been obtained using negative words, which were related to specific symptoms of the respective mental disorders (Besnier et al., 2011; Fear & Healy, 1996). On the neuronal level, the studies investigating brain areas activated during emotional processing revealed somewhat inconsistent results, showing involvement of the dorsolateral and medial PFC, anterior cingular cortex (ACC), bilateral inferior parietal lobe and superior temporal gyri (Compton et al., 2003; Dresler et al., 2012; Tupak et al., 2013). The aim of Study 1 was to investigate emotional processing and it's neuronal correlates in the dorsolateral prefrontal cortex (DLPFC).

In line with our initial hypothesis, individuals in both groups at risk for schizophrenia showed significantly decreased right DLPFC activation compared to the healthy controls for the negatively valenced words. This finding suggests a deficient prefrontal regulation system when negatively valenced words are processed. However, decreased DLPFC in individuals at risk for schizophrenia has been observed also for positively and neutrally valenced words, albeit it did not differ significantly from the healthy controls. This could be explained by a spillover effect from the negatively valenced words or the more general DLPFC dysfunctions associated with attentional processing (Dresler et al., 2012). Perhaps, the activation effects could have been stronger, had the negative words been more symptom specific.

Interestingly, the most prominent differences between the healthy controls and all individuals at risk for schizophrenia and bipolar disorder were found in the frontotemporal cortex (FTC), regardless of the valence of words. FTC has been associated with reading, language and semantic processing (Fiebach, Friederici, ller, & Cramon, 2002; Whitney et al., 2011). Therefore, these results point to general dysfunctions in reading and processing of the written words. Behavioral results seem to support this explanation, as negative correlations between FTC activation and performance measures were found. However, emotional Stroop does not directly assess reading and semantic processing. Therefore, a more specific task, for example one employing differentiation between words and pseudo-words (e.g., Fiebach et al., 2002) would be more advisable.

Study 1 delivered interesting results regarding PFC and FTC functioning in individuals at risk for schizophrenia and bipolar disorder. However, to our knowledge, no imaging studies with manifest patients have been published. Therefore, it is not possible to estimate whether the findings relate to the at-risk state or are underlying trait markers. Lack of correlations with psychopathology symptoms (including state anxiety) would suggest underlying neuropsychological and neurophysiological dysfunctions, which are state independent. Nevertheless, without studies investigating manifest patients and, in a further step, healthy first-degree relatives, this interpretation remains only theoretical.

6.2 Verbal Fluency Test

The aim of Study 2 was to investigate cognitive performance and PFC activation during VFT in individuals at risk for schizophrenia and bipolar disorder, and compare these findings with healthy controls. Applying fNIRS allowed for a simultaneous measure of performance and PFC activation during phonemic and semantic VFTs. VFT is a well-established task, which has often been employed in neuropsychological and imaging research (Costafreda et al., 2006; Henry, 2006). In the two versions of VFT, different word retrieval strategies are required to name as many nouns as possible that begin with a given letter or belong to a given semantic category in the phonemic and semantic VFT respectively. These different strategies are visible on neuronal level in different brain regions being activated. In an fNIRS study with healthy individuals, Tupak et al. (2012) reported increased PFC activation only during phonemic VFT and FTC activation during both phonemic and semantic VFT. However, contradictory findings were presented by Kubota et al. (2005), who described increased activation in the PFC in the semantic compared to the phonemic VFT, in healthy individuals. Nevertheless, these finings have not been replicated (Dieler et al., 2012; Ehlis et al., 2007; Tupak et al., 2012).

In line with our initial hypotheses and previous research, all individuals at risk for schizophrenia showed poorer performance in both types of VFT compared to the control group. Furthermore, individuals at ultra-high risk for schizophrenia showed decreased left PFC activation compared to the healthy controls during the phonemic VFT. These results show that the cognitive deficits in word production and word retrieval can be observed in the at-risk stage, before schizophrenia becomes fully manifest. Moreover, decreased PFC activation in the ultra-high risk group suggests a dysfunctional word-retrieval strategy specifically for the phonemic VFT compared to healthy individuals.

Unexpectedly, individuals at high risk for bipolar disorder showed increased left PFC activation, which was significantly higher compared to all individuals at risk for schizophrenia. Since individuals at risk for bipolar disorder did not differ form the healthy controls, it could suggest that their phonemic word-retrieval strategy is the same as the one of healthy individuals. However, it requires more effort to be implemented. Furthermore, these results indicate cognitive differences as well as different phonemic word-retrieval strategies reflected in the PFC activation between persons at risk for schizophrenia and bipolar disorder. These findings could be a first step to differentiate between the at-risk stages of the two disorders in the future.

Even though previous studies described decreased PFC activation during semantic VFT in manifest schizophrenia patients, no group differences were found in this study. This is not entirely unexpected, since category guided word-retrieval strategies show activation especially in the FTC (Damasio et al., 2004). In the current study, no group or task related differences in FTC activation were found (unpublished results). This could suggest that the dysfunctions observed in the at-risk stage for schizophrenia relate rather to the dopamine pathway, as only the PFC functioning is affected (Masana, Santana, Artigas, & Bortolozzi, 2012).

6.3 Limitations

The results presented in this dissertation have to be interpreted with caution, because of several limitations. Firstly, the group of individuals at risk for bipolar disorder was much smaller than the other at-risk groups, which might have affected the results. However, the homogeneity of variances was given in all analyses. Furthermore, post-hoc calculations showed that the power of the tests was not affected when the BIP group was removed from the analysis.

Secondly, the experimental groups were not perfectly matched based on age and IQ. The ultra-high risk group was significantly younger and showed lower IQ than the other groups. This was most likely caused by the sampling protocols. All at-risk individuals were included in the study, after they came to one of the early recognition centers, fulfilled the inclusion criteria, and were willing to participate in the study. The respective group was assigned only after the inclusion in the study. Therefore, we hypothesize that lower age and IQ are innate

characteristics of the ultra-high risk group. The individuals in this group are characterized by more severe psychopathology and it is possible that they possessed more pronounced deficits, which had caused the symptoms to manifest earlier. This assumption makes the use of analysis of covariance (ANCOVA) to account for the effects of age and IQ inappropriate and might skew the results (for details see G. A. Miller & Chapman, 2001). However, in a series of unpublished ANCOVAs it was shown that the effects of age and IQ do not have a significant influence on the results.

The third limitation concerns the age of the study participants. Since schizophrenia and bipolar disorder develop in adolescence and early adulthood, individuals between 13 and 35 years of age were included in the studies. At this age the frontal cortex still undergoes major developmental changes (Gogtay et al., 2004), which makes all the at-risk groups very heterogeneous and increases the variance of the results. However, it also gives a possibility to identify state and trait at-risk criteria.

Last but not least, some of the study participants were receiving antipsychotic or antidepressant medication, which poses a further limitation of this study. However, it has been shown that antipsychotic medication has little influence on frontal blood flow (Cuesta, Peralta, & Zarzuela, 2001), even if the use of medication may improve cognitive functioning (Hori et al., 2006; Meltzer & McGurk, 1999). Furthermore, use of medication (assessed with chlorpromazine equivalents) did not correlate significantly with brain activation in both studies.

6.4 Future directions

The findings presented in this dissertation show that neurophysiological and cognitive abnormalities are visible as early as the at-risk stage for schizophrenia and bipolar disorder. Furthermore, these findings suggest that cognitive task together with neuroimaging methods might be used as predictive biomarkers. However, the results of the studies presented here ought to be considered as preliminary and further research that could establish these investigated parameters as potential biomarkers is still needed.

First and foremost, one has to establish, if the marker is state or trait dependent. If the marker correlates with symptoms over time, it is a state marker, which could indicate a stage of the disorder and its progression. However, if the marker is stable over time and independent from

symptom severity, it is a trait marker, which could indicate increased risk of developing the disorder (Luck et al., 2011). A state marker linked to a specific genetic constellation should be present in patients and in healthy individuals. Both of these markers could be useful in early recognition of mental disorders.

Secondly, selectivity and specificity of a potential biomarker have to be addressed. Sensitivity is number of correctly recognized positive cases, whereas specificity is number of correctly recognized negative cases (Razafsha et al., 2015). A biomarker should be as sensitive and specific as possible. However, it is possible that cognitive-neural biomarkers, such as the tasks presented in this work, may be specific and sensitive only to a subgroup of patients with a given mental illness or to a condition, which varies across the diagnostic categories (Luck et al., 2011).

Most importantly, a potential biomarker has to be able not only to distinguish between groups of individuals, but also between single persons. However, large inter-individual variance is common in neurophysiological research (e.g., Glabus et al., 2003). Especially problematic is the variance resulting from differences between the individuals, which is related to methodological discrepancies or differences between individuals that are not related to the disorder of interest (Luck et al., 2011). Future research will have to address this issue on a methodological as well as on a clinical level, for example by introducing several predictors in a complex mathematical model.

In a one-year-follow-up project (data available), we want to investigate the stability of the results presented in this dissertation. It is of particular interest to examine the potential changes in the group differences: whether they remain stable, become more pronounced or disappear over time. Furthermore, it is known that some of the individuals progressed to manifest schizophrenia and bipolar disorder. Therefore, new groups will be created including individuals who progressed to manifest disorders and those still at risk for the respective disorders.

The results of the studies presented here did not deliver any conclusive results regarding the correlations of brain activation and performance with psychopathological symptoms. It has been already described that many of the study participants showed a cognitive improvement and their psychopathological symptoms declined within a year (Metzler et al., 2015).

Therefore, it is of interest to examine, whether and how these changes in psychopathology and neuropsychology influence brain activation, especially PFC functioning.

It is still a long way to identify biomarkers that can be used in early recognition of schizophrenia and bipolar disorder. Combining several biomarkers with assessment of psychopathological symptoms and genetic risk factors will yield the most promising results, as it has been shown by Brietzke et al. (2012). The biggest challenges that are being faced at the moment are adapting the use of potential biomarkers for single individuals and moving the use of biomarkers from pure research to clinical practice (Pickard, 2015; Razafsha et al., 2015). Furthermore, for the biomarkers to be used in clinical setting, the assessment methods have to be easy to apply and economical, which limits the use of the newest and often expensive technologies and turns towards including several markers in complex statistical models (Luck et al., 2011; Scarr et al., 2015).

6.5 Conclusions

The studies presented in this dissertation extend the current knowledge regarding the frontal brain functioning in the at-risk stage for schizophrenia and bipolar disorder. In line with our initial hypotheses, the results showed differences in the PFC functioning and in performance in the individuals at risk for schizophrenia and bipolar disorder and healthy controls. The individuals at risk for schizophrenia can be characterized by decreased performance in both emotional Stroop and VFT, which is reflected in decreased PFC and FTC activation during both tasks. The individuals at risk for bipolar disorder did not show any performance deficits. However, neurophysiological changes in PFC and FTC were observed in this group. These findings suggest that the pathological processes leading to manifest schizophrenia and bipolar disorder might be quite distinct.

Emotional Stroop and VFT both require PFC activation and employ different cognitive functions. Therefore, the PFC dysfunctions observed in both tasks indicate that the dysfunctions observed in the at-risk stage are rather broad and not limited to a single cognitive ability. Furthermore, looking at the two studies separately does not provide a full differentiation between the at-risk groups and healthy controls. A broader picture emerges only when the results of both studies are considered together. This speaks for including various cognitive tasks, risk factors and pathological symptoms to create a comprehensive test battery for early recognition procedures.

Even though promising, the results presented in this dissertation are still preliminary. The one-year follow-up analysis will give some answers regarding the stability of the results over time and may answer the question whether the PFC dysfunctions are a state or rather a trait marker. Furthermore, before these PFC dysfunctions can be used as a biomarker the validity, specificity and sensitivity have to be investigated.

This work is the first step in the long process of identifying potential biomarkers indicating at-risk stage of schizophrenia and bipolar disorder. Together with the assessment of clinical symptoms, easy to measure and reliable biomarkers could greatly influence the early recognition procedures and significantly decrease the duration of untreated or wrongly treated mental illnesses.

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Curriculum vitae

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EDUCATION

08/2013 – present	Doctoral candidate in Psychology University of Zurich, Institute of Psychology, Division of Neuropsychology
09/2010 – 07/2013	Bachelor of Science (BSc) in Psychology University of Zurich, Institute of Psychology
07/2011	European Summer School "Health Psychology" European Federation of Psychology Students Associations (EFPSA)
03/2009 – 07/2010	Master of Science (MSc) in Biology, Human Biology University of Zurich, Faculty of Science, Biology
10/2005 – 03/2009	Bachelor of Science (BSc) in Biology University of Zurich, Faculty of Science, Biology

PROFESSIONAL EXPERIENCE

07/2015 – present	Research associate University Hospital of Psychiatry Department for Psychiatry, Psychotherapy and Psychosomatics
10/2010 – 06/2015	Research associate Zurich Research Program for a Sustainable Development of Mental Health Survives (ZInEP), University Hospital of Psychiatry
09/2009 – 12/2009	Laboratory assistant University Hospital Zurich, Department of Sleep Medicine
11/2008 – 03/2009	Office assistant Accelopment, Zurich
10/2006 – 01/2007	Teaching assistant University of Zurich, Laboratory exercise for molecular and classical genetics

GRANTS

11/2014	Travel grant from Schweizerische Akademie der Geistes- und Sozialwissenschaften (SAGW)

PEER-REVIEWED PUBLICATIONS

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., . . . Kawohl, W. (submitted). Different frontal brain activation during verbal fluency test in individuals at risk for schizophrenia and bipolar disorder: A functional near-infrared spectroscopy study.

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., . . . Kawohl, W. (submitted). Frontal brain activity in individuals at risk for schizophrenia and bipolar disorder during the emotional Stroop task - An fNIRS study.

Holper, L., Aleksandrowicz, A., Müller, M., Ajdacic-Gross, V., Haker Rössler, H., Fallgatter, A., . . . Rössler, W. (submitted). Brain correlates of emotional interference assessed by functional near-infrared spectroscopy in persons with subclinical psychotic symptoms.

Holper, L., Aleksandrowicz, A., Müller, M., Ajdacic-Gross, V., Haker Rössler, H., Fallgatter, A., . . . Rössler, W. (accepted for publication in *Schizophrenia Research*). Brain correlates of verbal fluency in subthreshold psychosis assessed by functional near-infrared spectroscopy.

Rodgers, S., grosse Holtforth, M., Hengartner, M. P., Müller, M., Aleksandrowicz, A., Rössler, W., & Ajdacic-Gross, V. (2015). Serum Testosterone Levels and Symptom-Based Depression Subtypes in Men. *Frontiers in Psychiatry, 6*, 61. doi: 10.3389/fpsyt.2015.00061

Ajdacic-Gross, V., Müller, M., Rodgers, S., Warnke, I., Hengartner, M. P., Landolt, K., . . . Rössler, W. (2014). The ZInEP Epidemiology Survey: background, design and methods. *International Journal of Methods in Psychiatric Research, 23*(4), 451-468. doi: 10.1002/mpr.1441

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CONFERENCE PRESENTATIONS

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., Rössler, W., Kawohl, W. (2015) Different frontal brain activation during verbal fluency test in individuals at risk for schizophrenia and bipolar disorder: A functional near-infrared spectroscopy study. Free Communication presented at the 12th World Congress of Biological Psychiatry, Athens, Greece

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., Rössler, W., Kawohl, W. (2015) Frontal brain activation during emotional Stroop task in individuals at risk for schizophrenia and bipolar disorder using functional near-infrared spectroscopy. Poster presented at the 12th World Congress of Biological Psychiatry, Athens, Greece

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., Rössler, W., Kawohl, W. (2015) Frontal brain activity in the individuals at risk for schizophrenia: A brain electrical topography study. Poster presented at the 12th World Congress of Biological Psychiatry, Athens, Greece

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., Rössler, W., Kawohl, W. (2014, November). Frontal and temporal brain activity during a verbal fluency task in individuals at risk for psychosis – A functional near-infrared spectroscopy study. Free Communication presented at the Congress of the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN), Berlin, Germany

Aleksandrowicz, A., Hagenmuller, F., Haker Rössler, H., Heekeren, K., Theodoridou, A., Walitza, S., Rössler, W., Kawohl, W. (2014, October). Frontal brain activation during emotional Stroop task in individuals at risk for schizophrenia and bipolar disorder using fNIRS. Poster presented at the fNIRS 2014 Congress, Montreal, Canada

Aleksandrowicz, A., Rodgers, S., Müller, Kawohl, W., Rössler, W., Castelao, E., Vandeleur, C., Preisig, M., Ajdacic-Gross, V. (2014, June). Here there and everywhere: infectious diseases in childhood impact on psychiatric and neuropsychiatric disorders. Free communication presented at the 12th Meeting of the Swiss Society of Psychiatric Epidemiology, Lausanne, Switzerland

Ajdacic-Gross, V., Aleksandra Aleksandrowicz, Stephanie Rodgers, Mario Müller, Michael P. Hengartner, Wolfram Kawohl, Wulf Rössler, Martin Preisig (2014, May). Quite specific: Distinctive subtypes in specific phobia. Symposium presentation at the 17th Epidemiology and Social Psychiatry Meeting (EPA), Ulm, Germany